Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Athena Poppas, MD, FACC, President
Dipti Itchhaporia, MD, FACC, Vice President
Howard “Bo” T. Walpole, Jr., MD, MBA, FACC, Treasurer
Daniel M. Philbin, Jr., MD, FACC, Secretary and Board of Governors Chair
Cathleen C. Gates, Acting Chief Executive Officer

Viviany R. Taqueti, MD, MPH, FACC, Chair
Rhonda M. Cooper-DeHoff, MD, FACC
Prasad C. Gunasekaran, MD
Fadi G. Hage, MD, FACC
Islam Y. Elgendy, MD, FACC
Fred M. Kusumoto, MD, FACC
Renato D. Lopes, MD, PhD, FACC
Sandra M. Oliver-McNeil, DNP, ACNP-BC
John U. Doherty, MD, FACC
Syed Tanveer Rab, MBBS, MACC
Janice Sibley, MS, MA, ACC Executive Vice President, Education and Publishing Divisions
Justine Varieur Turco, MA, ACC Divisional Senior Director, Publishing

CORRESPONDENCE FOR AMERICAN COLLEGE OF CARDIOLOGY
All correspondence for the College, other than that related to JACC: Cardiovascular Imaging, should be sent to Resource Center, American College of Cardiology, 2400 N Street NW, Washington, DC 20037
ORIGINAL RESEARCH

LA Mechanics in Decompensated Heart Failure
Insights From Strain Echocardiography With Invasive Hemodynamics

Sébastien Deferm, MD,a,b,* Pieter Martens, MD,a,b,* Frederik H. Verbrugge, MD, PhD,a Philippe B. Bertrand, MD, PhD,a Jeroen Dauw, MD,a,b David Verhaert, MD,a Matthias Dupont, MD,a Pieter M. Vandervoort, MD,a,c Wilfried Mullens, MD, PhD,a,c

ABSTRACT

OBJECTIVES The aim of this study was to assess the effect of congestion and decongestive therapy on left atrial (LA) mechanics and to determine the relationship between LA improvement after decongestive therapy and clinical outcome in immediate or chronic heart failure with reduced ejection fraction (HFrEF).

BACKGROUND LA mechanics are affected by volume/pressure overload in decompensated HFrEF.

METHODS A total of 31 patients with HFrEF and immediate heart failure (age 64 ± 15 years, 74% male, left ventricular ejection fraction 20 ± 12%) underwent serial echocardiography during decongestive therapy with simultaneous hemodynamic monitoring. LA function was assessed by strain (rate) imaging. Patients were re-evaluated 6 weeks after discharge and prospectively followed up for the composite endpoint of heart failure readmission and all-cause mortality.

RESULTS LA reservoir function was markedly reduced at baseline and improved with decongestion (peak atrial longitudinal strain from 6.4 ± 2.2% to 8.8 ± 3.0% and strain rate from 0.29 ± 0.11 s⁻¹ to 0.38 ± 0.13 s⁻¹), independent of changes in left ventricular global longitudinal strain, LA end-diastolic volume, and mitral regurgitation severity (p < 0.001). Both measures continued to rise at 6 weeks (up to 13.4 ± 6.1% and 0.50 ± 0.19 s⁻¹, respectively; p < 0.001). LA pump strain rate only increased 6 weeks after discharge (–0.25 ± 0.12 s⁻¹ to –0.55 ± 0.29 s⁻¹; p < 0.010). Changes in LA mechanics correlated with changes in wedge pressure (r = -0.61; p < 0.001). Lower peak atrial longitudinal strain values after decongestion were associated with increased risk for the composite endpoint of heart failure and mortality (p < 0.019).

CONCLUSIONS LA reservoir and booster function, while severely impaired during immediate decompensation, significantly improve during and after decongestive therapy. Poor LA reservoir function after decongestion is associated with worse outcome. (J Am Coll Cardiol Img 2020;13:1107-15) © 2020 by the American College of Cardiology Foundation.

The pathophysiological contribution and prognostic impact of left atrial (LA) mechanics in heart failure are often underappreciated. More than solely being a passive extension of the left ventricle, the left atrium can be regarded as a dynamic continuum of the left ventricle with a principal role of ensuring left ventricular (LV) filling and cardiac performance by its reservoir, conduit, and booster pump function (1). This 3-phase role depends not only on LV diastolic and systolic function but also...

From the *Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; ‡Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; and the ‡Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium. *Drs. Deferm and Martens contributed equally to this work. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

Manuscript received September 10, 2019; revised manuscript received November 25, 2019, accepted December 5, 2019.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2019.12.008
METHODS

STUDY DESIGN. Patients with acutely decompensated HFrEF admitted in the heart failure intensive care unit of a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium) were prospectively included between 2011 and 2013 to undergo invasive hemodynamic monitoring and simultaneous echocardiography (4). Comprehensive echocardiographic data, laboratory data, and hemodynamic measurements were always obtained simultaneously in a congestive state (at admission in resting conditions on average 1 h after pulmonary artery catheter placement) and after optimization of cardiac filling pressures (pulmonary artery wedge pressure [PAWP] <18 mm Hg and central venous pressure <8 mm Hg), through decongestive therapy with diuretic agents and intravenous sodium nitroprusside switched to oral hydralazine and neurohormonal blockers per protocol (4). Six weeks after hospital discharge, patients were evaluated at the outpatient clinic with repeat echocardiography. In addition, the initial study cohort was followed up prospectively for the development of heart failure readmission and all-cause mortality.

The study complied with the Declaration of Helsinki, and the locally appointed ethics committee approved the research protocol. Written informed consent was obtained from every patient before any study-specific procedure was performed.

STUDY POPULATION. Patients were eligible if they were ≥18 years of age and presented with symptomatic decompensated HFrEF warranting invasive hemodynamic-guided therapy according to their treating cardiologist. Additional inclusion criteria were: 1) left ventricular ejection fraction (LVEF) ≥40%, restrictive LV filling pattern on echocardiography in addition to a right ventricular systolic pressure ≥40 mm Hg; and 2) agreement of the patient with the placement of a radial and pulmonary artery catheter (Swan-Ganz Continuous Cardiac Output Thermodilution Catheter 744HF75, Edwards Lifesciences, Irvine, California) for study purposes. Exclusion criteria after obtaining baseline hemodynamic measurements were: 1) PAWP <15 mm Hg; 2) mean pulmonary arterial pressure <25 mm Hg; 3) cardiac index ≥2.6 l/min/m²; 4) need for inotropic support or ventilator assist devices; 5) previous mitral valve intervention; and 6) insufficient imaging quality to allow adequate speckle-tracking echocardiography.

BASELINE HEMODYNAMIC MEASUREMENTS. At inclusion, the pulmonary artery catheter was placed with fluoroscopic guidance in the catheterization laboratory. Baseline hemodynamic measurements were performed in the supine position at end-expiration with the balloon-tipped pulmonary artery catheter at steady state 1 h after placement. During hemodynamic and echocardiographic measurements, an arterial and mixed venous blood sample was collected for blood gas analysis, used for the calculation of cardiac output/index according to the Fick equation (4).

IMAGE ACQUISITION AND STORAGE. Comprehensive two-dimensional (2D) echocardiographic examinations were performed with a commercially available system (IE33 Philips Medical Systems, Andover, Massachusetts) during stable electrocardiography recording at the same moment invasive hemodynamic assessments were performed. Standard 2D and Doppler echocardiographic images were acquired by experienced cardiac sonographers. Echocardiographic images were stored as DICOM files on a secured server and analyzed off-line, using third-party software Image arena version 4.6 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). All echocardiographic parameters were measured according to the American Society of Echocardiography guidelines (5). LV volumes and LVEF were measured by using the modified Simpson rule. Mitral regurgitation was graded as trace, mild, moderate, or severe by using an integrated approach, as recommended (6).

ASSESSMENT OF LA MECHANICS. LA maximum volume (at the end of ventricular systole) and LA minimum volume (at the end of LV diastole) were measured by using the modified Simpson rule. Furthermore, the 3-fold action of the left atrium (reservoir, conduit, and booster pump function) was assessed by using strain and strain rate imaging derived from 2D speckle-tracking echocardiography.
During immediate congestion, a restrictive mitral inflow pattern is found along a depressed mitral annulus septal ‘e’ and severely depressed left atrial (LA) reservoir and booster pump function. After decongestion and further follow-up until 6 weeks after hospital discharge, significant increments in LA reservoir function (peak atrial longitudinal reservoir strain [PALS]) appear. Booster pump strain rate (SR), a measure of LA contractile function, only increases significantly as of 6 weeks.

CVP = central venous pressure; ECG = echocardiography; MPAP = mean pulmonary artery pressure; MV = mitral valve; PAWP = pulmonary artery wedge pressure; RVSP = right ventricular systolic pressure; SR Res = strain rate reservoir; TDI = tissue Doppler-derived imaging; TR Vmax = maximum velocity of the tricuspid regurgitant velocity jet.
according to the EACVI/ASE/Industry Task Force recommendations to standardize deformation imaging (7). Offline speckle-tracking analysis of the phasic LA function was performed by using a commercially available software package (2D cardiac performance analysis, Image arena version 4.6). Peak atrial longitudinal strain (PALS) was determined as the peak positive strain value during late systole on the averaged longitudinal strain curve. In addition, the (positive) reservoir strain rate in late systole, the (negative) conduit strain rate in early diastole, and the (negative) pump strain rate were determined from the averaged LA longitudinal strain rate curve.

The Central Illustration summarizes the evolution of LA strain parameters in addition to conventional echocardiographic indices of diastolic function. Supplemental Table 1 presents the interobserver variability of LA functional measurements, illustrating overall excellent agreement (intraclass correlation coefficient >0.9 for strain [rate] measurements both in a congestive state and after decongestive therapy).

CLINICAL FOLLOW-UP. All patients were followed up prospectively for the development of heart failure readmissions or all-cause mortality. Heart failure readmissions were defined as unscheduled hospitalizations during which intravenous diuretic agents were administered because of signs and symptoms of congestion. Censoring occurred when the final patient had completed 1 year of follow-up.

STATISTICAL ANALYSIS. Categorical data are expressed as numbers and proportions and compared by using the chi-square test. Continuous variables are expressed as mean ± SD if normally distributed or median [interquartile range] if not. Normality was assessed by using the Shapiro-Wilk statistic. Repeated measurements were compared by using the paired Student’s t-test. To account for between-subject differences and adjust for co-variates (in-subject differences), an analysis of covariance model was built assessing changes in between-subject factors and within-subject factors. Pearson’s correlation was used to assess the relation between 2 or more continuous variables if parametric assumptions were met. Kaplan-Meier curves were constructed, with the log-rank test used to test differences in event rate for the combined endpoint of all-cause mortality and heart failure readmission. Statistical significance was always set at a 2-tailed probability level of <0.05. Statistics were performed by using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

STUDY POPULATION. A total of 37 patients were initially included in the prospective protocol; 6 patients were excluded from LA strain analysis due to insufficient quality of the LA image acquisition. Baseline characteristics of the patient population (N = 31) are summarized in Table 1. Patients were on average 64 ± 15 years of age; 77.4% were male with a mean LVEF of 20 ± 12%. There was an equal proportion of patients with an ischemic and a nonischemic etiology of heart failure. At the time of admission, patients were “cold and wet,” as reflected by a PAWP of 26 ± 7 mm Hg, a central venous pressure of 14 ± 7 mm Hg, and a cardiac index of 1.8 ± 0.5 l/min/m². Ten patients presented with atrial fibrillation at admission and remained in atrial fibrillation even after decongestion. Of the patients in sinus rhythm at study entry, none developed atrial arrhythmias thereafter. The use and doses of neurohumoral blocker therapy were similar for all patients after discharge.

Hemodynamic changes before and after decongestive therapy are summarized in Table 2. PAWP decreased to 15 ± 7 mm Hg (p < 0.001) and central venous pressure to 6 ± 5 mm Hg (p < 0.001). The median N-terminal pro-B-type natriuretic peptide level was 3,901 pg/ml (1,825 to 8,231 pg/ml) (Table 1) and 2,288 pg/ml (1,059 to 3,364 pg/ml) at admission and discharge, respectively. N-terminal pro-B-type natriuretic peptide levels at admission were comparable between patients with PALS after decongestion above the mean versus below the mean, although there was a trend toward lower values at discharge in the latter subgroup (p = 0.316 and p = 0.060, respectively).

LA FUNCTION BEFORE AND AFTER DECONGESTIVE THERAPY. At baseline, LA volume index was 69 ± 26 ml/m². Reservoir function was markedly reduced as assessed by PALS (6.42 ± 2.21%) and reservoir strain rate (0.29 ± 0.11 s⁻¹). Pump strain rate was -0.25 ± 0.12 s⁻¹ (Table 3). Baseline PALS and LV global longitudinal strain were moderately correlated (r = -0.58; p = 0.002). Patients with PALS below the sample mean exhibited significantly larger LA end-diastolic and end-systolic volumes (p < 0.001).

After decongestion, both PALS and reservoir strain rate increased significantly (6.42 ± 2.21% to 8.80 ± 3.00% and 0.29 ± 0.11 s⁻¹ to 0.38 ± 0.13 s⁻¹, respectively; p < 0.001 for both). The improvement in LA reservoir function was independent of changes in LV global longitudinal strain (p < 0.001), changes in
At baseline, no significant correlation was found between PALS and PAWP (p = 0.269) (Figure 2A). After decongestive therapy, there was a moderate correlation between PALS and PAWP (r = -0.50; p = 0.006) (Figure 2B). Larger decreases in PAWP during decongestion correlated with larger increases in PALS (r = -0.61; p < 0.001) (Figure 2C). Adjusted for LV end-diastolic volume, LV end-systolic volume, LV global longitudinal strain, and LA volume index, PALS after decongestion remained an independent predictor for PAWP (forward multivariate linear regression model; p = 0.033).

**PROGNOSTIC VALUE OF RESERVOIR FUNCTION ON HEART FAILURE HOSPITALIZATION AND ALL-CAUSE MORTALITY.** Mean follow-up was 655 ± 289 days. Thirteen patients were readmitted for immediate decompensated heart failure (n = 10 vs. n = 3 PALS after decongestion below and above the mean, respectively; log-rank test; p = 0.030). Five patients

| TABLE 1 Baseline Characteristics of the Study Population (N = 31) |
|---------------------------------------------------------------|
| Demographic characteristics and comorbidities                |
| Age, yrs                                                     | 64 ± 15 |
| Male sex                                                     | 24 (77.4) |
| Ischemic cardiomyopathy                                      | 15 (48.4) |
| NYHA functional class III/V                                  | 16 (51.6)/9 (29.0) |
| Obesity                                                      | 11 (35.5) |
| Hypertension                                                 | 15 (48.4) |
| Diabetes                                                     | 9 (29.0) |
| Dyslipidemia                                                 | 19 (61.3) |
| History of atrial fibrillation                                | 10 (32.3) |
| Clinical characteristics                                     |
| BMI, kg/m²                                                   | 28.1 ± 6.0 |
| Sinus rhythm                                                 | 22 (71.0) |
| eGFR, ml/min/1.73 m²                                         | 62.4 ± 21.5 |
| NT-proBNP, pg/ml                                             | 3,901 (1,825–8,231) |
| Heart failure medication                                     |
| ACE inhibitor or ARB                                         | 16 (51.6) |
| Hydralazine                                                  | 8 (25.8) |
| Beta-blocker                                                 | 23 (74.2) |
| MRA                                                         | 13 (41.9) |
| Loop diuretic                                                 | 18 (58.1) |
| Baseline echocardiographic parameters                        |
| LVEDV, ml                                                    | 229 ± 77 |
| LVESV, ml                                                    | 182 ± 74 |
| LV EF, %                                                     | 20 ± 12 |
| LV endoGLS, %                                                | -7.3 ± 3.5 |
| E, m/s                                                       | 0.9 ± 0.2 |
| A, m/s (if sinus rhythm)                                     | 0.4 ± 0.1 |
| E/A (if sinus rhythm)                                        | 2.6 ± 0.7 |
| MV deceleration time, ms                                     | 139.7 ± 42.1 |
| Mean E/e (septal and lateral)                                | 16.8 ± 6.6 |
| Moderate or higher MR                                        | 16 (51.6) |

Values are mean ± SD, n (%), or median (interquartile range).
ACEn = angiotensin-1-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BSA = body surface area; eGFR = estimated glomerular filtration rate; LV endoGLS = left ventricular endocardial global longitudinal strain; LVEDV = left ventricular end-diastolic volume; LV EF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; MV = mitral valve; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

MR/LA severity (p < 0.001), changes in LA end-diastolic volume (p < 0.001), or baseline LA end-diastolic volume (p = 0.001). As illustrated in Figures 1A and 1B, both PALS and reservoir strain rate continued to increase at 6 weeks after discharge (up to 13.44 ± 6.08% and 0.50 ± 0.19 s⁻¹; p < 0.001 for both compared with either baseline or discharge). Conversely, conduit and pump strain rate did not improve promptly after decongestion (p = 0.071 and p = 0.103). Only after 6 weeks, a significant improvement in LA contractility—assessed by booster pump strain rate—was assessed by booster pump strain rate, found (~0.25 ± 0.12 s⁻¹ at baseline to ~0.55 ± 0.29 s⁻¹ at 6 weeks; p < 0.010) (Figure 1C).

**TABLE 2 Resting Hemodynamic Variables at Admission and After Decongestive Therapy**

|                | Admission | After Decongestive Therapy | p Value |
|----------------|-----------|----------------------------|---------|
| Heart rate, beats/min | 84 ± 20   | 78 ± 12                    | 0.013*  |
| SBP, mm Hg      | 126 ± 23  | 112 ± 19                   | <0.001*|
| DBP, mm Hg      | 76 ± 15   | 59 ± 10                    | <0.001*|
| MAP, mm Hg      | 93 ± 14   | 77 ± 10                    | <0.001*|
| CVP, mm Hg      | 14 ± 7    | 6 ± 5                      | <0.001*|
| SPAP, mm Hg     | 58 ± 11   | 40 ± 16                    | <0.001*|
| DPAP, mm Hg     | 28 ± 8    | 18 ± 8                     | <0.001*|
| MAP, mm Hg      | 38 ± 8    | 26 ± 10                    | <0.001*|
| PAWP, mm Hg     | 26 ± 7    | 15 ± 7                     | <0.001*|
| Cardiac index, l/min/m² | 1.8 ± 0.5 | 2.2 ± 0.7                  | 0.002*  |

Values are mean ± SD. *Significant longitudinal change from baseline to follow-up.

CVP = central venous pressure; DBP = diastolic blood pressure; DPAP = diastolic pulmonary artery pressure; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PAC = pulmonary artery compliance; PAWP = pulmonary artery wedge pressure; SBP = systolic blood pressure; SPAP = systolic pulmonary artery pressure.

**TABLE 3 Functional and Mechanical LA Parameters at Baseline and After Decongestion and at 6 Weeks**

|                  | Baseline | After Decongestion | 6-Week Follow-Up |
|------------------|----------|--------------------|------------------|
| LVEDV, ml        | 108 ± 42 | 93 ± 43*          | 78 ± 34*†       |
| LAVI, ml/m²      | 69 ± 26  | 64 ± 25*          | 59 ± 18*        |
| LA endoGLS, %    | 6.04 ± 2.35 | 8.25 ± 3.27*     | 13.5 ± 5.90*†  |
| PALS, %          | 6.42 ± 2.21 | 8.80 ± 3.0*      | 13.44 ± 6.08*† |
| SR reservoir, s⁻¹| 0.29 ± 0.11 | 0.38 ± 0.13*     | 0.50 ± 0.19*†  |
| SR conduit, s⁻¹  | -0.40 ± 0.21 | -0.47 ± 0.21     | -0.52 ± 0.31   |
| SR pump, s⁻¹ (if sinus rhythm) | -0.25 ± 0.12 | -0.31 ± 0.10 | -0.35 ± 0.29† |

Values are mean ± SD. †p = 0.001 compared with baseline. *p = 0.05 compared with value after decongestion. p < 0.01 compared with baseline.
endoGLS = endocardial global longitudinal strain; EDV = end-diastolic volume; LA = left atrial; LAVI = left atrial volume index; PALS = peak atrial longitudinal reservoir strain; SR = strain rate.
died in the subgroup with lower decongested PALS, opposed to 1 in the other subgroup (log-rank test; \( p = 0.140 \)). Figure 3 shows the Kaplan-Meier curve for the combined endpoint of heart failure recurrence and all-cause mortality. Baseline PALS was not predictive (\( p = 0.471 \)). Lower PALS values after decongestion (i.e., below the sample mean) were associated with a higher event rate (log-rank test; \( p < 0.019 \)). In a forward conditional multivariable model incorporating LA volume index, LV end-diastolic volume, and LV global longitudinal strain, PALS after decongestion remained independently associated with the composite endpoint (hazard ratio: 0.78; 95% confidence interval: 0.62 to 0.97; \( p = 0.030 \)). These differences in outcome were despite largely comparable baseline patient characteristics, resting hemodynamic values, and echocardiographic features (Supplemental Table 2). Similarly, less recovery of PALS after decongestive therapy (ratio of delta PALS/PALS after decongestion below a median value of 33%) was associated with higher event rates (log-rank test; \( p < 0.038 \)) (Supplemental Figure 1). In contrast, conventional parameters such as mean E/e' or LA volume index after decongestion were not predictive of the combined endpoint (log-rank test; \( p = 0.091 \) and \( p = 0.067 \)).

DISCUSSION

This study adds novel information about the effects of decongestive therapy on alterations in LA mechanical function and its association with outcomes in advanced decompensated HFrEF. Key findings of this study are, first, decongestive therapy and afterload reduction acutely improved LA reservoir function, assessed by PALS and reservoir strain rate. Second, while immediate changes in PAWP during decongestive therapy correlated with immediate...
changes in LA reservoir function, intrinsic LA mechanics (including contractile function) improved incrementally up to 6 weeks after appropriate decongestion, even in advanced heart failure states. Third, PALS after decongestion was associated with PAWP, independent of LV and LA volumes. Lastly, greater improvement in PALS and a higher absolute PALS value after decongestion were independently associated with a lower risk for the composite endpoint of all-cause death or immediate heart failure recurrence. Thus, our data show that LA reservoir function is strongly impaired in immediate decompen-sated HFrEF but has the potential to recover in a subset of patients in the weeks after decongestive therapy, which is related to improved outcomes. These data indicate that effective decongestion is a prerequisite, yet no guarantee, to restore LA function.

**PATHOPHYSIOLOGY OF LA MECHANICAL FAILURE IN HFrEF.** Far beyond being a small transport chamber passively emptying into the left ventricle during diastole, the left atrium exerts a 3-phase function (reservoir, conduit, and booster pump) during the cardiac cycle to maintain cardiac performance (2,3) (Supplemental Figure 2, left-sided panel). In this regard, it is important to underscore the continuous dynamic interplay between LA and LV mechanics. The left atrium is excessively prone to volume and/or pressure overload in the context of increased LV filling pressures (8). As such, LA failure in the context of global heart failure may be the result of intrinsic atrial myopathy (9), altered loading forces (i.e., hypertension, immediate congestion), or maladaptive compensatory mechanisms (3). The latter refers to a short-term rise in contractile shortening when LA size increases following exposure to high filling volume (LA preload) or pressure (LA afterload) (Frank-Starling law at the atrial level) (Supplemental Figure 2, center panel). Ultimately, LA contractile function declines when the optimal threshold fiber length is exceeded (10,11) (Supplemental Figure 2, right-sided panel). Few studies have assessed LA mechanics by deformation imaging in HFrEF. PALS outperformed E/e’ as a predictor for LV end-diastolic pressure in advanced HFrEF (12) and proved to be a powerful prognosticator for the composite endpoint of heart failure rehospitalization and all-cause death in these subjects (13). Moreover, LA reservoir function at rest correlated strongly with impaired functional capacity during exercise (14). Importantly, all of these studies have focused on LA function in stable, compensated HFrEF. Instead, LA adaptation to pressure and volume overload has not been studied extensively.

**FIGURE 2 Correlations Between PALS and PAWP**

(A) No significant correlation was found between peak atrial longitudinal reservoir strain (PALS) and pulmonary artery wedge pressure (PAWP) during congestion. (B) A modest significant correlation was found between PALS and PAWP after decongestive therapy. (C) Differences between PALS and PAWP at baseline (wet) and after decongestive therapy correlate significantly. Abs = absolute.
This study offers novel information on LA mechanics measured simultaneously with invasive hemodynamic values in immediate heart failure, while evaluating the effect of decongestive therapy. LA reservoir function (according to PALS and reservoir strain rate) and booster pump function (booster pump strain rate) were markedly declined at baseline in a state of congestion, along with a restrictive mitral valve flow pattern and increased cardiac filling pressures. Adequate decongestion led to a significant increase in reservoir function (both PALS and reservoir strain rate). Importantly, this improvement was independent of changes in LV global longitudinal strain and LA end-diastolic volume (considering both are key drivers for LA expansion as well) (13,15,16). Six weeks after hospital discharge, an additional increase in mean LA reservoir function was found, advocating additional LA mechanical function improvement. Booster pump strain rate improved significantly only after 6 weeks.

Of note, PALS during hospitalization (both before and after decongestive therapy) was considerably lower in this study compared with previous studies reporting PALS in chronic HFrEF (13,14). These differences may relate to the additional insult (i.e., immediate decompensation warranting hemodynamic-guided therapy) to which the diseased left atrium is exposed. Previously, LA pressure-area relations illustrate reduced LA compliance in congestive heart failure with major effects on LA passive mechanical properties (V-loop) (17). In progressive heart failure with a restrictive filling pattern, the left atrium transitions from a storage and contractile chamber to a basic conduit (i.e., conduit function predominates, as illustrated by the pressure-volume loop in Supplemental Figure 2, right-sided panel) (8,18). Also, increased LV filling pressures (during immediate congestion) may act as a “second-hit” for LA booster pump mechanics already functioning at the tipping point of the Frank-Starling mechanism (8).

Heart failure therapy is able to decrease LV wall tension and LA afterload mismatch, which seems to relieve LA booster pump function in the failing heart (19,20). In addition to restoring LA preload reserve, arterial vasodilators have been shown to improve operative atrial distensibility in congestive heart failure (20). These data are consistent with the findings in our study, showing a significant rebound of LA reservoir and booster pump function. Most probably, LA mechanical recovery requires time. Booster pump strain rate only improved significantly after 6 weeks. PALS improved steadily to previously reported values in stable HFrEF after an event-free interval of 6 weeks.

Finally, our study found a significant relation between LA reservoir function after decongestion and the composite endpoint of all-cause mortality or immediate exacerbated heart failure. This effect may in part be explained by the contribution of impaired LA mechanics to circulatory failure, sodium retention, and possibly the facilitation or maintenance of atrial fibrillation (2,15).

STUDY LIMITATIONS. This single-center study is limited by the relatively small sample size, which hampers generalization of the effect of LA mechanics on hard clinical endpoints and possibly may explain the lack of significance of conventional echocardiographic parameters on these end points. Echocardiography-based LA strain measurements demand sufficient image quality to track the thin-walled left atrium in the far field and was therefore not feasible in all of the initially included patients. Third, measuring LA (dys)function by using deformation imaging has yet to achieve widespread acceptance. As such, intervendor variability and consensus on the normal reference values are currently not clearly defined. Interpretation of atrial
functional indices can be challenging, caused by the continuous interplay with the left ventricle and sensitivity to loading changes. However, assessing LA mechanics longitudinally during various loading conditions in HFrEF was the primary objective of this study.

CONCLUSIONS

This study assessed LA mechanics with simultaneous invasive hemodynamic variables in acutely decompensated HFrEF and evaluated the effect of decongestive therapy and afterload reduction. Immediate decompensated heart failure resulted in a markedly compromised reservoir and booster pump function. Adequate decongestive therapy was able to unload the left atrium, reflected by a significantly increased reservoir and pump function over time. Worse reservoir strain after decongestion was associated with a higher risk for the composite endpoint of heart failure recurrence or all-cause death.

REFERENCES

1. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC State-of-the-Art Review. J Am Coll Cardiol 2019;73:1961-77.
2. Triposkias F, Pieske B, Butler J, et al. Global left atrial failure in heart failure. Eur J Heart Fail 2016;18:1307-20.
3. Hoit BD. Left atrial size and function: Role in prognosis. J Am Coll Cardiol 2014;63:493-505.
4. Verbrugge FH, Dupont M, Bertrand PB, et al. Pulmonary vascular response to exercise in symptomatic heart failure with reduced ejection fraction and pulmonary hypertension. Eur J Heart Fail 2015;17:320-8.
5. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2015;16:232-71.
6. Zoghi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. J Am Soc Echocardiogr 2017;30:303-71.
7. Badano LP, Kolas TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: A consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2018;19:591-600.
8. Dernellis JM, Stefanidis CI, Zacharoulis AA, Toutouzas PK. Left atrial mechanical adaptation to long-standing hemodynamic loads based on pressure-volume relations. Am J Cardiol 1998;81:1138-43.
9. Guichard J-B, Nattel S. Atrial cardiomyopathy. J Am Coll Cardiol 2017;70:756-65.
10. Payne RM, Stone HL, Engellin EJ. Atrial function during volume loading. J Appl Physiol 1971;31:326-31.
11. Hoit BD, Shao Y, Gabel M, Walsh RA. Left atrial mechanical and biochemical adaptation to pacing induced heart failure. Cardiovasc Res 1995;29:469-74.
12. Cameli M, Sparla S, Losito M, et al. Correlation of Left Atrial Strain and Doppler Measurements with Invasive Measurement of Left Ventricular End-Diastolic Pressure in Patients Stratified for Different Values of Ejection Fraction. Echocardiography 2016;33:398-405.
13. Carluccio E, Biagioli P, Mengoni A, et al. Left atrial reservoir function and outcome in heart failure with reduced ejection fraction. Circ Cardiovasc Imaging 2018;11:e007696.
14. D’Andrea A, Caso P, Romano S, et al. Association between left atrial myocardial function and exercise capacity in patients with either idiopathic or ischemic dilated cardiomyopathy: A two-dimensional speckle strain study. Int J Cardiol 2009;132:354-63.
15. Ernbell M, Møller JE. Left atrial function in heart failure with reduced ejection fraction. Circ Cardiovasc Imaging 2018;11:e008427.
16. Ersbøll M, Andersen MJ, Valeur N, et al. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is Dependent on left ventricular longitudinal function and left atrial size. Circ Cardiovasc Imaging 2013;6:26-33.
17. Dernellis JM, Vyssoulis GP, Zacharoulis AA, Toutouzas PK. Acute changes of left atrial distensibility in congestive heart failure. Clin Cardiol 1998;21:28-32.
18. Pagel PS, Kehl F, Gare M, Hettrick DA, Kersten JR, Waltitger DC. Mechanical function of the left atrium new insights based on analysis of pressure-volume relations and doppler echocardiography. Anesthesiol J Am Soc Anesthesiol 2003;98:975-94.
19. Ito T, Suwa M, Kobashi A, Yagi H, Hirota Y, Kawamura K. Reversible left atrial dysfunction possibly due to afterload mismatch in patients with left ventricular dysfunction. J Am Soc Echocardiogr 1998;11:274-9.
20. Xie GY, Berk MR, Fiedler AJ, Sapin PM, Smith MD. Left atrial function in congestive heart failure: assessment by transmural and pulmonary vein Doppler. Int J Card Imaging 1998;14:47-53.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE LA mechanics are affected by loading conditions in heart failure and might contribute to ongoing sodium retention and circulatory failure. LA reservoir and booster pump function are markedly declined during congestion but can recover. Worse LA reservoir function after decongestion associates with adverse outcomes.

TRANSLATIONAL OUTLOOK: Future research studying LA failure in the context of global heart failure and its pathophysiological contribution to worse clinical outcome is needed.

ADDRESS FOR CORRESPONDENCE: Dr. Wilfried Mullens, Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. E-mail: wilfried.mullens@zol.be.

APPENDIX For supplemental tables and figures, please see the online version of this paper.
EDITORIAL COMMENT

Left Atrial Reservoir and Booster Function in HFrEF
Implications for Diastolic Function*

Thierry C. Gillebert, MD, PhD

In this issue of iJACC, Deferm et al. (1) reported on repeated analyses performed in a small cohort of patients with heart failure with reduced ejection fraction (HFrEF) (n = 31) with a mean EF of 20%. The patients were hospitalized for an acute heart failure syndrome. Invasive hemodynamics were performed after initial stabilization and repeated after decongestion, before hospital discharge. Echocardiographic assessment was performed after initial stabilization, after decongestion, and after 6 weeks of follow-up. Patients were treated according to current standards. These serial invasive and noninvasive measurements provided unique insight into the course of left atrial (LA) remodeling and function, with focus on reservoir and booster function. LA booster function is also known as pump or contractile function.

Acute heart failure resulted in markedly compromised reservoir function, independently of changes in left ventricular (LV) global longitudinal strain (GLS), LA volume index, and mitral regurgitation severity. Decongestive treatment unloaded the LA with a slightly increased reservoir function. Reservoir and booster function further improved in parallel at 6-week follow-up. Lower peak atrial longitudinal strain (PALS) values after decongestion were associated with an increased risk of the composite endpoint (heart failure re-admissions or all-cause mortality). The results are summarized and put into perspective in Figure 1. The evolution from initial assessment (‘1’) till after decongestion (‘2’) could be explained by the unloading therapy and might have been expected. The main novel finding was the further improvement of PALS (+50%) and of booster strain rate (+70%) from decongestion to 6-week follow-up (‘3’). This was a major finding that enhances our understanding of recovery after acute heart failure in a patient with HFrEF. For clinicians, it is not surprising that adequately treated patients improve over time, but this study shows us exactly why; at 6 weeks, recovery of LA booster function underlies, at least in part, the improved reservoir function. I still wonder to what extent LV GLS and stroke volume further improved over time as well and whether these factors participated in the recovery of LA reservoir function. These key confounders unfortunately were not reported.

The Russian physiologist Felix Meerson (2) developed the concept of 3 stages of heart failure on elaborate experimental models of aortic stenosis. The stages are: 1) overload, which is use of reserve capacity and recruitment of adaptive mechanisms; 2) compensatory remodeling that results in hypertrophy; and 3) exhaustion of the compensatory mechanisms and irreversible heart failure.

The concept was expanded by Grossman et al. (3), who described concentric hypertrophy in response to pressure overload and eccentric hypertrophy in response to volume overload. This approach was further integrated in contemporary cellular and molecular biology (4). Those efforts were directed at understanding what happened in the LV, with some research as well on the right ventricle. The LA has remained the forgotten chamber for decades. The remodeling of the LA is solely seen as a dilatation. This is because we have insufficient data on mal-adaptive hypertrophy and fibrosis of the LA in response to pressure and volume overload, respectively. LA pressure overload is the hallmark of diastolic dysfunction and elevated filling pressures.

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of iJACC or the American College of Cardiology.

From the Department of Cardiology, Ghent University and Ghent University Hospital, Ghent, Belgium. Dr. Gillebert has reported that he has no relationships relevant to the contents of this paper to disclose. The author attests they are in compliance with human studies committees and animal welfare regulations of the author’s institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.
Intervention (exercise, stress) or continuous elevation of filling pressures is the main trigger for atrial dysfunction and atrial fibrillation. The paper by Deferm et al. (1) illustrates Meerson’s paradigm and applies it to LA pressure overload in HFrEF. It reports both overload (LA pressures), remodeling (LA volume index [LAVI]) and function (reservoir and booster). After acute heart failure, severe LA remodeling and dysfunction can recover not only as a consequence of decongestion but also as a result of partially recovering atrial function. We go from exhaustion and failure to a condition of stabilization with a somewhat improved function. The recovery is partial. We remain far from the situation of compensated hypertrophy, and the patient remains quite vulnerable. A better recovery of LA function with time might be associated with a somewhat better prognosis. This deserves to be further investigated.

The LA contributes to systolic and diastolic LV function by its reservoir, conduit, and booster pump function (5). PALS quantifies the longitudinal expansion of the LA wall during systole and is a measure of LA reservoir function. When heart failure progresses, PALS linearly decreases. Interpretation of PALS may not always be that easy. PALS has been too long regarded as solely reflecting LV function and LA size (6,7). However, various determinants should be considered:

1. Longitudinal systolic LV function: during systole, the fibrotic atrioventricular ring that connects the atria and ventricles is moving toward the apex. Therefore, the LA reservoir function is intimately related to longitudinal LV function (8), as evaluated by annular excursion, anular s’ velocity, or (global) longitudinal LV strain.
2. LAVI: LA strain is expressed as a percentage of initial length. It matters if the LA under scrutiny is enlarged or not. For a given stroke volume, and, in steady-state conditions (atrial filling volume), strain will be reduced in an enlarged LA.
3. Transmitral flow volume: LA strain depends on transmitral flow so that cardiac output and heart rate are confounding factors. In the presence of mitral regurgitation, atrial filling volume will increase and so will LA strain.
4. LA booster function: during early systole, relaxation of the atrial muscle causes the atrioventricular ring to move toward the ventricles, at the onset of muscular contraction (8). When atrial contraction (pump or booster function) becomes dysfunctional, this affects early systolic atrial relaxation and stroke volume, hence on reservoir function and PALS.
5. LA filling pressures and stiffness: LA strain depends on operating stiffness. If filling pressures are elevated and/or if the wall has an increased intrinsic stiffness, systolic filling of the atria will cause a disproportional increase in pressures, thereby limiting pulmonary venous return and engorging pulmonary venous circulation.

To summarize, atrial reservoir function and PALS not only depend on LV longitudinal systolic function and LA volume, but on transmitral flow volume, atrial booster function, and atrial filling pressures (stiffness) as well.

In busy clinical practices, evaluating diastolic function and LV filling pressures with echocardiography remains challenging. No single measurement is good enough for providing a reliable answer to diverse clinical requests. The prevailing 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations use a panel of measurements that can be integrated with the clinical context (9). The limitations of the recommendations could be addressed by integrating novel measurements; PALS appears to be the most attractive. As a sensitive parameter, PALS could be incorporated into routine evaluation of LV diastolic dysfunction, more specifically in patients who are

![Figure 1: LA Reservoir Function (PALS) in HFrEF](image-url)
classified in the indeterminate diastolic dysfunction group, using the independent prognostic algorithm (10). Several published and ongoing investigations address the independent prognostic value of PALS. For example, in stable patients with HFReF, PALS remained significantly associated with outcome and provided incremental predictive value, even after multivariable adjustment (including LA volume and LV GLS) (11). The study by Deferm et al. (1) further confirms the confidence we already have in PALS for evaluating diastolic function, not only as an early marker (as stated previously), but as a biomarker in the follow-up of our patients, each patient being their own control.

For integrating LA booster function in the evaluation of diastolic function, one has to be more careful because booster function will have a biphasic course when disease proceeds. The booster function (atrial contraction) first increases, compensating for decreased conduit function, then decreases as a consequence of both elevated LA pressures and contractile dysfunction. Rossvoil and Hatle (12), who pioneered noninvasive assessment of diastolic function, were the first to point toward the importance of evaluating LA contractile function. The analysis of pulmonary venous reversal during a compensatory increase of booster function was shown to be a reliable indicator of elevated end-diastolic pressure. However, proper recording of the pulmonary venous flow signal requires experience and remains demanding. Hatle (Oh et al. [13]) was also the first to indicate how failure of LA booster function affects mitral inflow and pulmonary venous signals, and therefore, assessment of diastolic function (13). The paper by Deferm et al. (1) offers a potentially more reproducible way to directly assess LA booster function. These investigators brilliantly demonstrate how severe congestion depresses LA booster function, both by increasing afterload and by inducing contractile dysfunction. This dysfunction may persist for weeks after decongestion. Although reservoir function turns out to be a sensitive marker of early diastolic dysfunction, the combination of low reservoir and low booster function indicates more severe heart failure, with an expectedly increased occurrence of atrial fibrillation, thrombotic complications, acute heart failure syndrome, and death.

In summary, the study under scrutiny, with its the well-designed setup and the repeated observations, provides unique insight on how LA function in patients with HFReF is affected by decongestion and how 6 weeks of congestion control may result in improved LA booster and reservoir function.

ADDRESS FOR CORRESPONDENCE: Dr. Thierry C. Gillebert, Department of Cardiology 8K12IE, Heymans Campus, Ghent University, De Pintelaan, 185, B-9000 Ghent 9000, Belgium. E-mail: thierry.gillebert@ugent.be.

REFERENCES

1. Deferm S, Martens P, Verbrugge FH, et al. LA mechanics in decompensated heart failure: insights from strain echocardiography with invasive hemodynamics. J Am Coll Cardiol Img 2020;13:1107-15.
2. Meerson FZ. Compensatory hyperfunction of the heart and cardiac insufficiency. Circ Res 1962;10:250-8.
3. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56-64.
4. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet 2006;367:356-67.
5. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. J Am Coll Cardiol 2019;73:1961-77.
6. Erbøll M, Andersen MJ, Valeur N, et al. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. Circ Cardiovasc Imaging 2013;6:26-33.
7. Solomon SD, Biering-Sorensen T. LA strain when ejection fraction is preserved a new measure of diastolic function? J Am Coll Cardiol Img 2017;10:744-6.
8. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. Circulation 1999;100:427-36.
9. Nagues SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
10. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA strain for categorization of LV diastolic dysfunction. J Am Coll Cardiol Img 2017;10:735-43.
11. Carluccio E, Biagioli P, Mengoni A, et al. Left atrial reservoir function and outcome in heart failure with reduced ejection fraction. Circ Cardiovasc Imaging 2018;11:e007696.
12. Rossvoil O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. J Am Coll Cardiol 1993;21:1687-96.
13. Oh JK, Appleton CP, Hatle LK, Nishimura RA, Seward JB, Tajik AJ. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 1997;10:246-70.

KEYWORDS: booster, contractility, diastolic function, heart failure, HFReF, left atrium, left ventricle, reservoir, strain.
ORIGINAL RESEARCH

Interpatient Similarities in Cardiac Function
A Platform for Personalized Cardiovascular Medicine

Márton Tokodi, MD,a,b Sirish Shrestha, MSc,c Christopher Bianco, MD,d Nobuyuki Kagiyama, MD, PhD,a Grace Casaclang-Verzosa, MD,d Jagat Narula, MD, PhD,d Partho P. Sengupta, MD, DMa

ABSTRACT

OBJECTIVES The authors applied unsupervised machine-learning techniques for integrating echocardiographic features of left ventricular (LV) structure and function into a patient similarity network that predicted major adverse cardiac event(s) (MACE) in an individual patient.

BACKGROUND Patient similarity analysis is an evolving paradigm for precision medicine in which patients are clustered or classified based on their similarities in several clinical features.

METHODS A retrospective cohort of 866 patients was used to develop a network architecture using 9 echocardiographic features of LV structure and function. The data for 468 patients from 2 prospective cohort registries were then added to test the model's generalizability.

RESULTS The map of cross-sectional data in the retrospective cohort resulted in a looped patient network that persisted even after the addition of data from the prospective cohort registries. After subdividing the loop into 4 regions, patients in each region showed unique differences in LV function, with Kaplan-Meier curves demonstrating significant differences in MACE-related rehospitalization and death (both p < 0.001). Addition of network information to clinical risk predictors resulted in significant improvements in net reclassification, integrated discrimination, and median risk scores for predicting MACE (p < 0.05 for all). Furthermore, the network predicted the cardiac disease cycle in each of the 96 patients who had second echocardiographic evaluations. An improvement or remaining in low-risk regions was associated with lower MACE-related rehospitalization rates than worsening or remaining in high-risk regions (3% vs. 37%; p < 0.001).

CONCLUSIONS Patient similarity analysis integrates multiple features of cardiac function to develop a phenotypic network in which patients can be mapped to specific locations associated with specific disease stage and clinical outcomes. The use of patient similarity analysis may have relevance for automated staging of cardiac disease severity, personalized prediction of prognosis, and monitoring progression or response to therapies.

(J Am Coll Cardiol Img 2020;13:1119–32) © 2020 by the American College of Cardiology Foundation.

Cardiovascular disease continues to be a leading cause of death worldwide (1). One of the major research priorities is to prevent adverse clinical events and hospitalization by risk factor management and by earlier detection of subclinical cardiac dysfunction. This research has led to a plethora of noninvasive approaches, with diverse technical underpinnings, to assess various

From the aDivision of Cardiology, West Virginia University Heart & Vascular Institute, Morgantown, West Virginia; bHeart and Vascular Center, Semmelweis University, Budapest, Hungary; and the cDivision of Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Sengupta has been a consultant for Heartsciences, Ultromics Ltd., and Kencor Health. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Jeroen J. Bax, MD, was Guest Editor on this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

Manuscript received August 2, 2019; revised manuscript received October 31, 2019, accepted December 19, 2019.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2019.12.018
and often overlapping aspects of cardiac function. For example, assessment of left ventricular (LV) systolic and diastolic function is an integral part of evaluating patients with subclinical or overt cardiac disease (2). However, a diagnostic imaging protocol can produce numerous parameters, each with its strengths and limitations (3). Several of these parameters are routinely used in clinical cardiology in conjunction with the 4 functional class stages of the New York Heart Association (NYHA) and the American College of Cardiology/American Heart Association (ACC/AHA) classification of heart failure. However, due to the lack of unanimity on the combination and use of these parameters to depict a single patient or a group of patients with similar characteristics, there is a paramount need to develop a staging method that can integrate multiple tests and diagnostic variables at the point of care.

In the present study, we explore topological data analysis (TDA) (4), a state-of-the-art data analytical approach that provides well-founded mathematical, statistical, and algorithmic methods to present the underlying geometric structures in data. It can be used in an unsupervised machine learning pipeline to compare multiple variables and clusters similar patients into nodes. A node connects with other nodes with edges if the same patients are clustered into >1 nodes. This allows us to summarize the complex data to a simple connected patient similarity network that can be visualized to attain novel insights into disease mechanisms (5,6). TDA has been successfully used to derive mechanistic insights from biological datasets in disciplines such as oncology, genomics, immunology, diabetes, and pre-clinical spinal cord injury (7-13). We applied the TDA-based network analysis to detect patient similarity patterns using a cross-sectional multi-parametric echocardiographic dataset. Accordingly, we pooled echocardiographic data from both ambulatory and hospitalized settings to develop a broad cross-sectional representation of patients across different stages of cardiac disease that can be identified readily on a patient–patient similarity network. We subsequently investigated the prognostic value of the topological network and explored whether the longitudinal course of disease observed could be tracked along the topological map to assess the risks of cardiac events in an index patient.

METHODS

DATA. There were 2 parts to our study. First, we developed a broad cross-sectional representation of patients across different stages of cardiac disease as a primary cohort by pooling patients from a retrospective study and 2 prospective registries. The network topology was first developed from the retrospective study. The addition of prospective data was used as a step for validating the persistence and stability of network topology.

Second, after the stability of the network shape was confirmed, we tested the personalized prediction for a new patient to be represented on this network structure by including a second cohort of patients who had 2 echocardiographic evaluations (secondary cohort) for clinically indicated reasons. As patients underwent 2 echocardiographic examinations, the change in the location of these patients over the network was monitored to understand whether the network also represented a change in cardiac disease staging.

STUDY POPULATION. A flowchart of the study population, inclusion and exclusion criteria are provided in Supplemental Figure 1. The retrospective group included a convenience sample of 866 outpatients (age 65 ± 17 years; 387 men and 479 women) in sinus rhythm who were referred for echocardiographic assessment of cardiac function between March 2013 and December 2015 at the Icahn School of Medicine at Mount Sinai (New York, New York). The prospective groups included 468 patients (age 55 ± 15 years; 195 men and 273 women) enrolled between July 2017 to February 2018 in 2 ongoing patient registries at West Virginia University (Morgantown, West Virginia) that followed 2 prospective trials (Analysis of Surface EKG Signals to Identify Myocardial Dysfunction in Patients at Risk for Coronary Artery Disease, NCT02560168; and Evaluation of Cardiopulmonary Diseases by Ultrasound, NCT02248831). The pooled patients from the retrospective study and the 2 prospective registries formed the primary cohort of patients used for developing the patient–patient similarity network.

For personalized patient predictions, we further tested the model in a secondary cohort of 96 patients (age 58 ± 15 years; 49 men and 47 women) from the prospective registries who had 2 consecutive echocardiographic examinations. Follow-up data for this cohort were collected after the second echocardiographic assessment. The additional details of comprehensive echocardiographic evaluations performed according to published guidelines (14) is
listed in the Supplemental Appendix. The institutional review board approved the study protocol, and all study participants in the prospective studies provided written informed consent.

**TDA.** We applied TDA to detect patterns in multidimensional echocardiographic parameters by studying the geometrical structure obtained from the network that signified a compressed representation of high-dimensional data (5) for patient similarity analysis. The notion of expressing the shape of data using TDA was extensively validated and successfully applied to different areas of health sciences (7,10–12,15). In the created topological network, nodes represented a cluster of patients, whereas edges connected nodes that contained patients who existed in both nodes. Nodes were color-coded based on the average value of the parameter of interest (e.g., ejection fraction [EF] or LV mass) of the clustered patients in the node. The nodes were colored red for the most extreme abnormal values, whereas they were colored blue for the maximum normal value. There were a gamut of colors for the average values in between.

TDA was performed using the cloud based Ayasdi Workbench v7.4 (Ayasdi Inc., Menlo Park, California). Nine echocardiographic parameters were used to create the topological network, namely, EF, LV mass index, early diastolic transmitral flow velocity (E), late diastolic transmitral flow velocity (A), E/A ratio, early diastolic relaxation velocity (ê), E/ê ratio, left atrial volume index, and tricuspid regurgitation peak velocity. The steps in generating the TDA network is provided in Figure 1. After the network was created in the primary cohort (containing retrospective and prospective cohorts), we trained a random forest-based classifier (16) using the echocardiographic data of the primary cohort to predict the region each patient from the secondary cohort might belong to. This allowed us to predict the characteristics of the patients and the outcomes the patient might have experienced. Additional details for the TDA can be found in the Supplemental Appendix.

**CLINICAL OUTCOMES, ENDPOINTS, AND STAGING.** Patient electronic medical records were reviewed for post-echocardiographic follow-up. Hospitalizations were classified based on the International Classification of Diseases-10th Revision coding. Endpoints were defined as death from a major adverse cardiac event (MACE) (defined as myocardial infarction, acute coronary syndrome, acute decompensated heart failure, cardiac arrest, or arrhythmia) and first MACE-related rehospitalization. The time to each endpoint was measured from the date of the echocardiographic examination used in the study. Clinical cardiac disease staging was performed using NYHA functional class assessment, ACC/AHA heart failure staging, and assessment of the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score. The ability of the MAGGIC score to predict death and cardiovascular hospitalization events related to MACE was well validated (17,18).
TABLE 1  Clinical and Echocardiographic Characteristics of the Retrospective Cohort

|                        | Retrospective Cohort (n = 866) | Region I (n = 177) | Region II (n = 138) | Region III (n = 286) | Region IV (n = 212) | Overall p Value |
|------------------------|---------------------------------|-------------------|-------------------|---------------------|---------------------|----------------|
| **Demographics**       |                                 |                   |                   |                     |                     |                |
| Men                    | 387 (45)                        | 73 (41)           | 39 (28)*          | 102 (36)*           | 142 (67)*           | <0.001         |
| Age, yrs               | 66 (54-79)                      | 49 (37-59)*       | 64 (58-72)*       | 78 (67-86)*         | 66 (55-80)*         | <0.001         |
| Body mass index, kg/m² | 26.8 (23.6–30.4)                | 25.9 (23.0–29.8)  | 25.7 (22.5–29.4)  | 27.0 (23.8–30.3)    | 27.5 (24.3–31.4)    | 0.013          |
| Hypertension           | 441 (51)                        | 48 (27)*          | 54 (39)†          | 189 (66)*           | 126 (59)†           | <0.001         |
| Hyperlipidemia         | 358 (41)                        | 37 (21)*          | 45 (33)*          | 153 (53)*           | 99 (47)             | <0.001         |
| Diabetes mellitus      | 178 (21)                        | 16 (9)*           | 14 (10)†          | 79 (28)*            | 60 (28)†            | <0.001         |
| COPD                   | 61 (7)                          | 4 (2)             | 14 (10)           | 25 (9)              | 15 (7)              | 0.012          |
| Tobacco abuse          | 377 (44)                        | 76 (43)           | 50 (36)           | 122 (43)            | 105 (50)            | 0.282          |
| History of CKD         | 214 (25)                        | 18 (10)*          | 18 (13)†          | 96 (34)*            | 62 (29)†            | <0.001         |
| **Clinical outcomes**  |                                 |                   |                   |                     |                     |                |
| MACE rehospitalization | 147 (17)                        | 8 (5)*            | 10 (7)*           | 77 (27)*            | 45 (21)             | <0.001         |
| MACE death             | 10 (1)                          | 0 (0)             | 0 (0)             | 3 (1)               | 5 (2)†              | 0.083          |
| **Echocardiography**   |                                 |                   |                   |                     |                     |                |
| LVEF, %                | 62 (57–67)                      | 63 (59–66)‡       | 65 (61–68)*       | 64 (60–68)*         | 56 (45–74)*         | <0.001         |
| LV mass index, g/m²    | 85 (67–106)                     | 66 (58–77)*       | 64 (58–76)*       | 93 (78–115)*        | 105 (87–129)*       | <0.001         |
| E, m/s                 | 0.79 (0.60–0.90)                | 0.73 (0.63–0.88)† | 0.70 (0.60–0.80)* | 0.80 (0.70–1.00)*   | 0.80 (0.60–1.00)†   | <0.001         |
| A, m/s                 | 0.76 (0.60–1.00)                | 0.58 (0.50–0.67)* | 0.86 (0.72–0.93)* | 1.11 (0.91–1.25)*   | 0.61 (0.49–0.75)*   | <0.001         |
| E/A                    | 0.90 (0.80–1.20)                | 1.30 (1.10–1.50)* | 0.80 (0.70–0.90)* | 0.80 (0.70–0.90)*   | 1.25 (1.00–1.90)*   | <0.001         |
| é, cm/s                | 6.0 (4.4–7.6)                   | 9.0 (8.0–11.0)*   | 6.7 (6.0–7.0)*    | 4.3 (4.0–5.0)*      | 5.7 (4.5–7.0)†      | <0.001         |
| E/é                    | 12.5 (9.2–17.9)                 | 8.3 (7.1–9.9)*    | 10.4 (8.5–12.0)*  | 18.2 (14.5–24.5)*   | 13.8 (10.4–19.5)*   | <0.001         |
| LA volume index, ml/m² | 34 (27–43)                      | 28 (22–34)*       | 27 (22–33)*       | 38 (31–48)*         | 42 (33–55)*         | <0.001         |
| TR peak velocity, m/s  | 2.30 (2.00–2.70)                | 2.10 (1.90–2.30)* | 2.20 (2.00–2.50)‡ | 2.50 (2.20–2.80)*   | 2.40 (2.10–2.84)*   | <0.001         |

Values are n (%) or median (interquartile range). *p < 0.001. †p < 0.01. ‡p < 0.05 between the region and the remaining regions, Kolmogorov-Smirnov test. Overall p values are calculated using analysis of variance or Kruskal-Wallis test.

A = late diastolic transmural flow velocity; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; é = early diastolic relaxation velocity at septal mitral annular position; E = early diastolic transmural flow velocity; EF = ejection fraction; LA = left atrial; LV = left ventricular; MACE = major adverse cardiovascular event(s); TR = tricuspid regurgitation.

**STATISTICAL ANALYSIS.** Between-group comparisons were performed using Pearson’s chi-square test or Fisher exact test (for categorical variables), and analysis of variance, Kruskal-Wallis test or Kolmogorov-Smirnov test (for continuous variables); use of the preceding statistical tests to compare patient groups within the topological network was previously performed (10,19). Correlations between categorical variables were computed using Goodman and Kruskal’s γ coefficient. The rates of hospitalization and survival were analyzed with Cox proportional hazard models, Kaplan-Meier curves, and the log-rank test. Cox proportional hazard models were constructed to elucidate independent prognostic values of region information after adjustment with ACC/AHA heart failure stage, NYHA functional class, and the MAGGIC risk score. Furthermore, to evaluate improvement of Cox proportional hazard models by adding region information to these risk predictors, integrated discrimination improvement, net reclassification improvement, and median improvement in risk score were calculated using R package survIDINRI version 1.1-1 (R Foundation, Vienna, Austria) (20,21). A p value of <0.05 was considered statistically significant. We used R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses.

**RESULTS**

Clinical characteristics of the study population are shown in Tables 1 and 2.

**CONTINUUM OF CARDIAC FUNCTION.** The use of TDA to create a patient–patient similarity network in the retrospective dataset resulted in the formation of a looped structure. After the addition of cases from the prospective data, the loop was persistent, which validated that the phenotypic network loop structure of the network model was intrinsic to the data and not an artifact. The combined network was used for discovering feature distributions and developing associations with clinical and outcome data. We noted that echocardiographic variables followed a gradually changing pattern throughout the loop (Figure 2). Moving counterclockwise, starting from the top of the loop, we observed gradually decreasing EF and é values and increasing LV mass index, E/é ratio, left atrial volume index, and tricuspid regurgitation peak velocity values. In addition to the echocardiographic features, cardiovascular risk factors, MACE-related
TABLE 2 Clinical and Echocardiographic Characteristics of the Prospective Cohort

|                  | Prospective Cohort (n = 468) | Region I (n = 165) | Region II (n = 113) | Region III (n = 59) | Region IV (n = 112) | Overall p Value |
|------------------|------------------------------|-------------------|--------------------|---------------------|---------------------|-----------------|
| **Demographics** |                              |                   |                    |                     |                     |                 |
| Male             |                              |                   |                    |                     |                     |                 |
| Age, yrs         |                              |                   |                    |                     |                     |                 |
| Body mass index, kg/m² | 30.7 (25.7–36.5)  | 29.5 (25.1–37.1)  | 31.5 (25.1–37.8)  | 28.6 (24.4–36.3)  | 31.0 (27.3–34.9)  | 0.509           |
| SBP, mm Hg       | 126 (114–140)               | 122 (110–135)     | 124 (115–140)      | 135 (122–147)      | 127 (111–147)      | <0.001          |
| DBP, mm Hg       | 75 (68–82)                  | 75 (69–83)        | 76 (68–81)         | 72 (68–80)         | 73 (66–79)         | 0.252           |
| Hypertension     | 318 (68)                    | 88 (53)           | 79 (70)            | 45 (76)            | 91 (81)            | <0.001          |
| Hyperlipidemia   | 337 (72)                    | 101 (61)          | 89 (79)            | 47 (80)            | 84 (75)            | 0.003           |
| Diabetes mellitus| 115 (25)                    | 22 (13)           | 26 (23)            | 16 (27)            | 43 (38)            | <0.001          |
| **Medications**  |                              |                   |                    |                     |                     |                 |
| ACEI/ARB         | 158 (34)                    | 38 (23)           | 43 (38)            | 25 (42)            | 45 (40)            | 0.003           |
| Beta-blocker     | 160 (34)                    | 34 (21)           | 29 (26)            | 23 (39)            | 66 (58)            | <0.001          |
| Calcium channel blocker† | 71 (17)      | 20 (12)           | 23 (20)            | 8 (16)             | 13 (21)            | 0.208           |
| Statin†          | 166 (41)                    | 47 (28)           | 53 (47)            | 26 (53)            | 28 (44)            | 0.001           |
| **Clinical staging and outcomes** |                  |                   |                    |                     |                     |                 |
| NYHA functional class, I/II/III | 268/123/62/15 | 123/32/9/1†       | 63/44/6/0†         | 25/25/9/0*         | 44/19/35/4        | <0.001          |
| ACC/AHA stage, A/B/C/D | 122/168/17/7     | 80/43/2/0†       | 26/37/50/0         | 4/28/26/0*         | 8/48/50/6       | <0.001          |
| MAGGIC score     | 11 (7–16)                   | 9 (5–12)          | 12 (9–15)          | 14 (11–20)         | 18 (9–26)        | <0.001          |
| MACE rehospitalization | 38 (8)         | 3 (2)             | 4 (4)              | 5 (8)              | 26 (23)           | <0.001          |
| MACE death       | 9 (2)                       | 0 (0)             | 1 (1)              | 0 (0)              | 8 (7)            | <0.001          |
| **Echocardiography** |                          |                   |                    |                     |                     |                 |
| LVEF, %          | 62 (57–66)                  | 62 (59–65)*       | 65 (62–68)         | 63 (59–67)         | 54 (39–60)        | <0.001          |
| LV mass index, g/m² | 74 (60–95)                 | 64 (55–75)†       | 64 (56–76)†        | 83 (71–102)*       | 108 (89–136)*     | <0.001          |
| E, m/s           | 0.79 (0.65–0.94)            | 0.81 (0.69–0.92)† | 0.69 (0.60–0.82)† | 0.81 (0.63–0.94)† | 0.90 (0.69–1.11)‡ | <0.001          |
| A, m/s           | 0.71 (0.57–0.87)            | 0.62 (0.52–0.72)† | 0.86 (0.75–0.94)† | 0.99 (0.85–1.16)‡ | 0.58 (0.42–0.70)‡ | <0.001          |
| E/A              | 1.10 (0.82–1.40)            | 1.28 (1.10–1.50)† | 0.82 (0.73–0.91)† | 0.79 (0.70–0.93)† | 1.43 (1.10–2.10)‡ | <0.001          |
| é, cm/s          | 7.0 (5.3–9.0)               | 9.1 (8.0–11.0)†   | 7.0 (6.0–8.0)      | 5.0 (4.0–6.5)       | 5.0 (4.0–6.5)      | <0.001          |
| E/e              | 10.5 (8.4–14.4)             | 8.4 (6.9–10.1)†   | 10.2 (9.0–11.9)†   | 15.5 (13.4–19.4)†  | 16.5 (11.2–25.0)†  | <0.001          |
| LA volume index, ml/m² | 29 (22–37)             | 25 (21–31)        | 24 (19–29)         | 36 (28–43)         | 42 (34–56)        | <0.001          |
| TR peak velocity, m/s | 2.19 (1.90–2.50)   | 2.01 (1.70–2.30)‡ | 2.10 (1.81–2.35)† | 2.40 (2.10–2.63)‡  | 2.42 (2.11–2.90)‡ | <0.001          |

Values are n (%), median (interquartile range), or n. *p < 0.01; †p < 0.001; ‡p < 0.05; between the region and the remaining regions, Kolmogorov-Smirnov test. Overall p values are calculated using analysis of variance or Kruskal-Wallis test. |Data available only for 274 patients. #Data available only for 407 patients.

ACC/AHA = American College of Cardiology/American Heart Association; ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; CVA = cerebrovascular accident; DBP = diastolic blood pressure; HF = heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; NYHA = New York Heart Association; SBP = systolic blood pressure; other abbreviations as in Table 1.

rehospitalization, and death also showed accumulation in distinct sections of the loop (Table 1).

Upon seeing the gradations of echocardiographic variables, and to create clinically useful categories, we measured multidimensional Euclidean distance of nodes using 9 echocardiographic parameters that were used to create the network (Supplemental Appendix). The distance was used to create the groups—which was correlated with the gradation of the variables—on the network and subsequently collated based on clinical characteristics into 4 regions (Central Illustration). The 4 groups were chosen for reaching equivalence to 4 empiric categories of symptoms or disease class used in clinical cardiology (NYHA functional classes I to IV and ACC/AHA heart failure class A to D). Patients in each region showed unique differences in clinical characteristics (Central Illustration, Tables 1 and 2, Supplemental Tables 1 and 2). Notably, progressing from the first to the fourth region, an increasing trend was seen in age and prevalence of underlying risk factors and comorbidities. LVEF remained preserved in the first to third regions; however, it was significantly reduced in the fourth region (p < 0.001). LV mass
progressively increased, and diastolic function parameters progressively worsened from region I to IV. We found a correlation between the regions and both NYHA functional classes ($\gamma = 0.47; p < 0.001$) and ACC/AHA stages ($\gamma = 0.52; p < 0.001$) in the prospective cohort, which showed more symptomatic patients in the third and fourth regions than in the first region (Figure 3A).

**ASSOCIATION OF REGIONS WITH MACE.** The median follow-up time in the primary cohort was 309 days (quartile 1 to 3: 100 to 531 days). A total of 207 (16%) patients were observed to have MACE-
related hospitalizations, and 19 (1%) patients died due to MACE during follow-up. The number of MACE-related hospitalizations increased progressively from regions I to IV (\(p < 0.001\)), with MACE-related deaths seen only in the third and fourth regions (\(p < 0.001\)).

The Kaplan-Meier curves for MACE-related rehospitalization in the regions differed significantly (\(p < 0.001\)) (Figure 4A). Patients in the fourth region had a >5-fold increased risk of re-hospitalization (hazard ratio [HR]: 5.89; 95% confidence interval [CI]: 3.39 to 10.24; \(p < 0.001\)), whereas patients in the third region had a >6-fold increased risk of re-hospitalization (HR: 6.88; 95% CI: 3.98 to 11.90; \(p < 0.001\)) compared with the first region. Subjects in the second region did not have a significantly increased risk of hospital admission due to MACE (HR: 1.45; 95% CI: 0.72 to 2.93; \(p = 0.301\)) compared with those in the first region. The number of MACE-related deaths was low in the first and second regions, whereas the probability of death was significantly higher in the third and fourth regions than in the first region (\(p < 0.001\)) (Figure 4B).

**INDIVIDUALIZED PATIENT PREDICTIONS.** Individualized patient predictions for clinical stages, severity, and future adverse events were tested in a secondary cohort analysis. Detailed demographics

---

**CENTRAL ILLUSTRATION** The Looped Network of Cardiac Dysfunction

Multiparametric echocardiographic datasets were used to develop a patient–patient similarity network using topological data analysis. Nodes indicate ≥1 patient who have similar echocardiographic characteristics, and nodes including similar patients are connected by edges. The color of nodes has been colorized with the mean ejection fraction (EF) of the node. Moving counterclockwise along with the gray arrow starting from the top of the loop, 4 regions were identified with different clinical presentations and outcomes. Region I consisted mostly of patients with risk factors but no obvious symptoms or disease. Patients in region II had more cardiac risk factors (especially hypertension [HTN]) with impaired left ventricular LV relaxation. Region III showed presence of patients with advanced diastolic dysfunction and heart failure with preserved EF (pEF) and pulmonary HTN, but region IV included patients with heart failure with reduced EF with increased LV mass, left atrial volume and pulmonary pressures. Although the map is developed using cross-sectional data, distinct regions of the networks correspond to distinct parts of the disease, along which patients can move on the map, signaling progression, treatment, and recovery of the disease. DM = diabetes mellitus; E/A = early to late diastolic transmitral flow velocity ratio; E/é = early diastolic transmitral flow to annular velocity ratio; HLD = hyperlipidemia; LAVi = left atrial volume indexed to body surface area; LVMi = LV mass indexed to body surface area; TRV = tricuspid regurgitation velocity.

Tokodi, M. et al. J Am Coll Cardiol Img. 2020;13(5):1119–32.
and the region comparison in this cohort are shown in Table 3 and Supplemental Table 3. After predicting the region membership of patients from the secondary cohort using the random forest classifier, the same tendency was observed for the probability of MACE-related rehospitalizations in the regions as was those in the primary cohort (Figure 4C, Supplemental Table 3). Subjects predicted to be in the fourth region had a >2-fold increased risk of MACE-related rehospitalization (HR: 2.75; 95% CI: 1.27 to 4.59; p = 0.010), whereas those belonging to the third and second regions were not associated with a significantly increased risk compared with those in the first region (HR: 0.95; 95% CI: 0.42 to 2.11; p = 0.890; and HR: 0.17 95% CI: 0.02 to 1.22; p = 0.078, respectively). Patients in the first region were free of any MACE. A correlation of NYHA functional classes and ACC/AHA stages with regions was also observed (γ = 0.56 and γ = 0.67; both p < 0.001, respectively), which indicated that more symptomatic patients were found in the fourth region than in other regions (Figure 3B).

We also wanted to demonstrate whether changing the location of a patient on the loop was associated with worsening or improvement of cardiac function. To illustrate the motion of patients on the loop, the predicted regions of the first and second echocardiograms were compared (Figure 5). Both
Kaplan-Meier curves of the 4 regions: (A) major adverse cardiovascular event(s) (MACE)-related rehospitalization in the primary cohort, (B) MACE-related death in the primary cohort, and (C) MACE-related rehospitalization in the secondary cohort. Abbreviation as in Figure 1.

DISCUSSION

The notion of patient similarity is a growing idea in personalized predictive analytics to support clinical assessment (10,22-25). Patient similarity is a method that can empower precision medicine to stratify patients into clinically relevant subgroups (22). Such subgroup identification generally involves the use of unsupervised machine learning methods for clustering patients (26). However, most clustering techniques discretize the continuous patient data to develop discrete groups, using arbitrary thresholds. In contrast, TDA refers to a collection of powerful geometric approaches that integrate complex high-dimensional data to develop a patient–patient similarity network. The network involves partial clustering, which allows cluster overlaps that illustrate the entire study population as a continuous network of similar patients. This method can allow us to capture the notion of connectivity and continuum to describe the different stages of a disease.

Using retrospectively and prospectively collected echocardiography data from 1,334 patients, we illustrated, for the first time, the potential role of a patient–patient similarity network for mapping cardiac dysfunction without the constraint of any a priori diagnostic system in varying degrees of LV structural and functional remodeling. Specifically, the TDA model in our analysis clustered the multi-parametric data without using a hierarchical structure.

echocardiograms in 13 patients were in low-risk regions (region I or II), whereas those in 63 patients were in the high-risk region (region III or IV). Fifteen patients showed improvement (moved from region III and/or IV to region I and/or II) in echocardiographic results, and 5 patients showed worsening (moved from region I and/or II to region II and/or IV) echocardiographic results. Improvement or staying in the low-risk regions was associated with lower MACE-related rehospitalization rates after the second echocardiogram was performed than worsening or staying in high-risk regions (3% vs. 37%; p < 0.001).

DISCRIMINATION AND RECLASSIFICATION. The incremental value of the topological regions was assessed in the prospective cohort. Even after adjustment with NYHA functional class, ACC/AHA heart failure stages, and MAGGIC scores, the predictive value of being in region IV was consistently significant with a 8- to 10-fold risk (Table 4). Net reclassification improvement, integrated discrimination improvement, and median improvement in risk score consistently showed that adding region information to NYHA functional class, ACC/AHA stage, and MAGGIC score significantly improved the prediction of the MACE-related events (Table 4). A combination of NYHA functional class (symptoms) and region information (cardiac function) performed better than that of the ACC/AHA stage, which also accounted for symptoms and cardiac function (C-index: 0.819 vs. 0.720).
or branching tree (4) but rather meaningfully represented the geometry of the data based on the similarity of the patients. Remarkably, the nodes clustered to produce a network in the form of a loop. Moreover, this loop demonstrated the relationships with the outcome of interest, which suggested a valid method of risk stratification for patients. We further illustrated the potential value of this loop for individualized prediction. Using a group of patients with longitudinally collected echocardiographic studies in which the patients were sampled in different stages of cardiac dysfunction, our analysis suggested that this looped space might also represent the periodic or recurrent behavior of the disease, thereby tracing the path that patients traveled through cycles of worsening cardiac function and recovery.

**PATIENT SIMILARITY VERSUS AN AVERAGE PATIENT.** Echocardiography remains the most versatile tool in clinical practice, offering an ever-increasing array of measurements. Although novel multivariate data-driven analytic approaches to stratifying cardiac dysfunction have been recently made available (27), the integration of clinical and echocardiographic data for precision phenotyping has been arduous using traditional techniques.

Classically, studies and results are based on meticulous experimental designs and statistical analyses to produce exhaustive results for an average
patient. However, no two patients are alike, making it difficult to generalize study results for average patients to actual patients with cardiac dysfunction. To this end, novel bioinformatics and machine-learning approaches have been suggested to help support integration of high-dimensional data for rapid medical decision-making (28–31).

The concept of the patient similarity network using TDA has been shown in well-known studies, such as those aiming to subgroup patients with diabetes (10), to identify individuals resistant to malaria infections (15), and patients with pre-clinical traumatic brain and spinal cord injury (11). TDA has specifically enabled real-time exploration of the concept of disease space. For example, Torres et al. (15) demonstrated a similar loop in analyzing disease tolerance to malaria in mice and humans and stratified the resilience of patients based on the size of the loop through the disease space. Similarly, we demonstrated a gradual change in echocardiographic variables throughout the disease cycle that outlined similarity among patients and that described different phenotypes of cardiac functions in the disease space. Despite the abundance and complexity of echocardiographic features, distinct paths emerged for the patients with cardiac dysfunction in clockwise or counterclockwise directions on
provide a strong foundation for why a provider could rely on this simplified staging scheme. Moreover, the TDA characterization system allows identifying patients on a disease map much like the Global Positioning System; such illustrated steps can help with automated classification, risk stratification, and monitoring progression or response to therapies. Such decision support systems are critically needed not only for clinical care but also for clinical trials in which heterogeneity of disease presentation affects patient matching and discovery of novel therapies.

STUDY LIMITATIONS. The follow-up duration and patient sample size for patients with reduced EFs was modest and potentially averted us from capturing a greater number of cardiac events to test the applicability, disease trajectory over time, and ability of our model to predict measurable isolated endpoints. Furthermore, specific therapeutic interventions that targeted any specific region on the loop or types of therapies that could change the patients’ prognoses were not included in the study and would be a logical next step that would be required to address in future studies. Addition of biomarkers and novel echocardiographic parameters, such as strain and strain rate, could provide an added benefit to the model and should also be investigated in the future.

CONCLUSIONS

TDA may have broad implications on developing clinical risk stratification schemes using

### Table 4

Independency and Incremental Value of Regions Upon Clinical Risk Predictors

| Model with NYHA functional class + regions: C-index 0.819 vs. 0.749 for model without regions | Model Improvement† |
| --- | --- |
| | Adjusted HR* |
| | HR | 95% CI | p Value |
| Region II | 2.20 | 0.53–9.21 | 0.280 |
| Region III | 1.90 | 0.92–16.46 | 0.064 |
| Region IV | 8.87 | 2.53–31.05 | <0.001 |
| Model with ACC/AHA stage + regions: C-index 0.815 vs. 0.720 for model without regions | Model Improvement† |
| | Adjusted HR* |
| | HR | 95% CI | p Value |
| Region II | 1.91 | 0.45–8.00 | 0.380 |
| Region III | 3.72 | 0.88–15.77 | 0.074 |
| Region IV | 12.39 | 3.71–41.35 | <0.001 |
| Model with MAGGIC score + regions: C-index 0.815 vs. 0.775 for model without regions | Model Improvement† |
| | Adjusted HR* |
| | HR | 95% CI | p Value |
| Region II | 2.01 | 0.48–8.43 | 0.340 |
| Region III | 2.92 | 0.67–12.76 | 0.160 |
| Region IV | 8.16 | 2.25–29.58 | 0.001 |

*Summarizes hazard ratio (HR) for each region adjusted by NYHA functional class, ACC/AHA stage, and Meta-Analysis Global Group in Chronic heart failure (MAGGIC) score, respectively. †Summarize model improvement by adding region information upon each risk predictors. CI = confidence interval; IDI = integrated discrimination improvement; MIRS = median improvement in risk score; NRI = net reclassification improvement; other abbreviations as in Table 2.

the loop based on the progression, treatment, and recovery of the disease.

**CLINICAL IMPLICATIONS.** There are several pathophysiological and clinical implications for our study. First, the continuity of our patient similarity network suggested the pathophysiological classification of cardiac dysfunction should be viewed as a continuum rather than as arbitrary divisions of the patient population into discrete subgroups as heart failure with reduced, mid-range, or preserved EF. Measures of LV systolic and diastolic function did not exhibit abrupt changes at any level of cardiac function, but they covered a gradual and continuous spectrum, creating an overlapping and interconnected spectrum of disease phenotypes that was previously suggested but not shown (32). Second, the 4 regions of the loop showed incremental value over NYHA functional class, ACC/AHA stages, and commonly used risk scores (e.g., MAGGIC risk score), which suggested the clinical usefulness of this approach in patient risk stratification. Finally, unlike the consensus-driven algorithms (e.g., NYHA functional class and ACC/AHA stage) that first use expert knowledge and then develop the stages and decision pathways, the computational technique described in this study learns automatically and requires no a priori knowledge or training to develop meaningful disease representation. This ability to integrate multiple parameters pragmatically to define patient phenotypes and to reproduce known clinical knowledge provides a strong foundation for why a provider could rely on this simplified staging scheme. Moreover, the TDA characterization system allows identifying patients on a disease map much like the Global Positioning System; such illustrated steps can help with automated classification, risk stratification, and monitoring progression or response to therapies. Such decision support systems are critically needed not only for clinical care but also for clinical trials in which heterogeneity of disease presentation affects patient matching and discovery of novel therapies.
patient–patient similarity networks. TDA can be used for an integrated assessment of multiple echocardiographic parameters that measure the extent of cardiac structural and functional remodeling. Moreover, such topological networks may be a viable data analytical approach to trace the progression of cardiac dysfunction in patients as they travel through cycles of compensation and decompensation within a looped disease space. Overall, identifying diverse cardiac phenotypes brings us one step closer to precision medicine.

ADDRESS FOR CORRESPONDENCE: Dr. Partho P. Sengupta, Heart & Vascular Institute, West Virginia University, 1 Medical Center Drive, Morgantown, West Virginia 26506-8059. E-mail: partho.sengupta@wvumedicine.org.

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics’ 2017 update: a report from the American Heart Association. Circulation 2017;135:e146–603.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–200m.
3. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:1–39.e14.
4. Lum PY, Singh G, Lehman A, et al. Extracting insights from the shape of complex data using topology. Sci Rep 2013;3:1236.
5. Carlsson G. Topology and data. Bulletin of the American Mathematical Society 2009;46:255–308.
6. Singh G, Memoli F, Carlsson G. Topological methods for the analysis of high dimensional data sets and 3D object recognition. Proc Eurographics Sym Point-Based Graphics 2007:91–100.
7. Nicolau M, Levine AJ, Carlsson G. Topology based data analysis identifies a subgroup of breast cancers with a unique mutational profile and excellent survival. Proc Natl Acad Sci U S A 2011;108:7265–70.
8. Camara PG, Rosenbloom DIS, Emmett KJ, Levine AJ, Rabdan R. Topological data analysis generates high-resolution, genome-wide maps of human recombination. Cell Syst 2016;3:83–94.
9. Lakshmikanth T, Olin A, Chen Y, et al. Mass cytometry and topological data analysis reveal immune parameters associated with complications after allogeneic stem cell transplantation. Cell Rep 2017;20:2238–50.
10. Li L, Cheng W-Y, Glicksberg BS, et al. Identification of type 2 diabetes subgroups through topological analysis of patient similarity. Sci Transl Med 2015;7:311ra74.
11. Nielson JL, Paquette J, Liu AW, et al. Topological data analysis for prediction in preclinical spinal cord injury and traumatic brain injury. Nat Commun 2015;6:8581.
12. Hinks T, Zhou X, Staples K, et al. Multidimensional endotypes of asthma: topological data analysis of cross-sectional clinical, pathological, and immunological data. Lancet 2015;385:542.
13. Hinks TSC, Zhou X, Staples KJ, et al. Innate and adaptive T cells in asthmatic patients: relationship to severity and disease mechanisms. J Allergy Clin Immunol 2015;136:323–33.
14. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.
15. Torres BY, Oliveira JHM, Thomas Tate A, Ruth P, Cummock K, Schneider DS. Tracking resilience to infections by mapping disease space. PLoS Biol 2016;14:e1002436.
16. WO2019006213A1 - Systems and methods for topological data analysis using nearest neighbors - Google Patents. Available at: https://patents.google.com/patent/WO2019006213A1/en. Accessed October 25, 2019.
17. Rich JD, Burns J, Freed BH, Maurer MS, Burkhoff D, Shah SJ. Meta-Analysis Global Group in Chronic (MAGGIC) heart failure risk score: validation of a simple tool for the prediction of morbidity and mortality in heart failure with preserved ejection fraction. J Am Heart Assoc 2018;7:e009594.
18. Simpson J, Iundt PS, Silva Cardoso J, et al. Comparing LC2696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: an analysis of mortality and morbidity in PARADIGM-HF. J Am Coll Cardiol 2015;66:2059–71.
19. Casacalang-Verzosa G, Shresta S, Khalil M, et al. Network tomography for understanding phenotypic presentations in aortic stenosis. J Am Coll Cardiol Img 2018;11:236–48.
20. Long Q, Xu J, Osunkoya AO, et al. Global transcriptome analysis of formalin-fixed prostate cancer specimens identifies biomarkers of disease recurrence. Cancer Res 2014;74:3228–37.
21. Uno H, Tian L, Cai T, Kohane IS, Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. Stat Med 2013;32:2430–42.
22. Parimbelli E, Marini S, Sacchi L, Bellazzi R. Patient similarity for precision medicine: a systematic review. J Biomed Inform 2018;83:87–96.
23. Zhang P, Wang F, Hu J, Sorrentino R. Towards personalized medicine: leveraging patient similarity and drug similarity analytics. AMIA Jt Summits Transl Sci Proc 2014:32–6.
24. Sharafoddini A, Dubin JA, Lee J. Patient similarity in prediction models based on health data: a scoping review. JMIR Med Informatics 2017;5:e7.
25. Ng K, Sun J, Hu J, Wang F. Personalized predictive modeling and risk factor identification using patient similarity. AMIA Jt Summits Transl Sci Proc 2015:132–6.
26. Kagiyama N, Sirosh S, Peter DF, Sengupta PP. Artificial intelligence: practical primer for clinical research in cardiovascular disease. J Am Heart Assoc 2019;8:e012788.
27. Omar AMS, Bansal M, Sengupta PP. Advances in echocardiographic imaging in heart failure with reduced and preserved ejection fraction. Circ Res 2016;119:357–74.

COMPETENCY IN MEDICAL KNOWLEDGE: A patient similarity network integrated echocardiographic parameters of cardiac structure and function to develop a looped network in which patients could be mapped precisely to specific disease stage and clinical outcomes. This network representation allowed automated classification of cardiac function and personalized prediction of MACE in an individual patient.

TRANSLATIONAL OUTLOOK: Patient similarity analysis can be combined with machine learning approaches to offer a practical solution for personalized risk stratification and may enable identification of patient populations with similar risk and those who are likely to respond to targeted therapies.

PERSPECTIVES
28. Antman EM, Loscalzo J. Precision medicine in cardiology. Nat Rev Cardiol 2016;13: 591-602.

29. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. N Engl J Med 2012;366:489-91.

30. Krittanawong C, Zhang HJ, Wang Z, Aydar M, Kitai T. Artificial intelligence in precision cardiovascular medicine. J Am Coll Cardiol 2017;69: 2657-64.

31. Samad MD, Ulloa A, Wehner GJ, et al. Predicting survival from large echocardiography and electronic health record datasets: optimization with machine learning. J Am Coll Cardiol Img 2019;12:681-9.

32. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation 2011; 123:1996-2004.

KEY WORDS echocardiography, patient similarity, topological data analysis

APPENDIX For an expanded Methods section as well as a supplemental figure and tables, please see the online version of this paper.
EDITORIAL COMMENT

Individualized Patient Risk Stratification Using Machine Learning and Topological Data Analysis*

Arnold C.T. Ng, MBBS, PhD,a,b Victoria Delgado, MD, PhD,c Jeroen J. Bax, MD, PhDc

Originally associated with the 18th-century mathematician Leonhard Euler, topology is a discipline in mathematics that studies shapes. One of the key ideas in topology is that the properties of shapes are invariant (i.e., unchanging) when deformed (e.g., a circle, an ellipse, and a hexagon are all topologically identical in that they are all “loops,” and any of these shapes can be obtained by deforming and stretching it). In topological data analysis (TDA), data points from large datasets are summarized into nodes, and the relationships between these nodes are connected by a line (also called an “edge”), thereby forming a large network of nodes connected by edges. This network has a particular “shape,” and typical network shapes are either “loops” (continuous circular segments) or “flares” (long linear segments) (1). Groups within these network shapes can be arbitrarily partitioned into segments with similar properties to identify patterns within the data, and they can be compared with other groups within the network using standard statistical techniques. Because these network shapes are invariant under deformations, one of the strengths of TDA is that it is less sensitive to noise and can detect patterns that can be missed by other analysis techniques such as principal-component analysis, multidimensional scaling, and cluster analysis (1).

TDA can be combined with machine learning, which involves computer algorithms that adjust and learn from input data. These algorithms can automatically divide a large dataset into clusters of smaller datasets such that those within the same cluster group are more similar to one another than to those in other clusters (e.g., echocardiograms from normal subjects vs. those of patients with heart failure) (2). In unsupervised machine learning, no a priori knowledge of the expected outcome is incorporated, and the computer algorithm uses only the content of the input data to discover any possible underlying structure. Such combined machine learning and TDA techniques can be used to identify novel classification systems or offer further insights into the natural history of diseases. In the first ever application of TDA in cardiovascular research, Casaslang-Verzosa et al. (3) described the natural history of aortic stenosis, which has 2 distinct moderate stenosis phenotypic expressions as it progresses from mild to severe stenosis (i.e., moderate aortic stenosis with normal vs. reduced ejection fraction).

In this issue of JACC, the same group (4) report on an evaluation of a large number of patients with a wide range of cardiac diseases at different stages of severity. Using unsupervised machine learning with TDA, 4 subgroups of patients were automatically identified with distinct differences in major adverse cardiac event (MACE) outcomes on the basis of standard echocardiographic parameters such as left ventricular ejection fraction, mass, and so on.
Identifying patients within each individual subgroup provided incremental risk stratification compared with traditional risk scoring such as New York Heart Association functional class.

The investigators should be commended as pioneers, bringing machine learning and state-of-the-art TDA into clinical cardiovascular research and developing novel risk stratification tools in the growing field of big data, electronic medical records, and artificial intelligence. The strengths of the present study are the large number of patients from different retrospective and prospective datasets, validation of their topological network shape using the prospective cohort, and including a longitudinal cohort to predict individual patient risk as they move from 1 subgroup to another as their disease severity changes over time. “Traditional” risk stratification presents a hazard ratio or an odds ratio for an “average” patient. In contrast, one of the most important clinical implications of this study is the ability of machine learning and TDA to automatically present individual patient risk profiles on the basis of similarities with other patients within the topological network.

However, several important questions remain unanswered. First, there are nodes that do not fit into the network, as demonstrated in the Central Illustration, and no information is provided on the characteristics of these patients. Therefore, not all patients’ data can be automatically compressed into a node to fit the topological network.

Second, the data used to form the network are simple and crude echocardiographic measures. The data do not include newer imaging techniques such as strain imaging, identification of subclinical coronary atherosclerosis on cardiac computed tomography, and scarring or interstitial fibrosis on cardiac magnetic resonance. Many of these techniques are already routinely used in clinical practice. Moreover, the network had limited information on patient diagnosis and therapeutic interventions such as device therapies, revascularizations, and so on. These variables will clearly have an impact on MACE outcomes for individual patients.

Finally, the investigators suggest that heart failure should be viewed as a continuum instead of arbitrary divisions into reduced, midrange, or preserved left ventricular ejection fraction. However, a long line of research had demonstrated the futility of therapies such as beta-blockers, angiotensin-converting enzyme inhibitors, and so on, for patients with heart failure with preserved ejection fraction. This strongly suggests a different pathophysiology compared with those with reduced left ventricular ejection fraction. As such, one should not confuse the association between subgroups of patients (with a particular pattern of echocardiographic parameters) and the corresponding MACE rates with direct causality.

In summary, Tokodi et al. (4) used a “new” mathematical modeling technique (i.e., TDA) with unsupervised machine learning to map the “shape” of a large echocardiographic dataset. The shape of the network can identify patterns in our echocardiographic measurements (e.g., left ventricular ejection fraction, mass, filling pressures) associated with different MACE rates. This study represents an initial stepping-stone in developing more complex and comprehensive cardiac risk stratification models using unsupervised machine learning fed with large datasets. Using novel mathematical modeling techniques such as TDA, clinicians may be able to provide individualized risk stratification for patients at different stages of their disease.

**ADDRESS FOR CORRESPONDENCE:** Dr. Jeroen J. Bax, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: j.j.bax@lumc.nl.

**REFERENCES**

1. Lum PY, Singh G, Lehman A, et al. Extracting insights from the shape of complex data using topology. Sci Rep 2013;3:1236.
2. Seetharam K, Shrestha S, Sengupta PP. Artificial intelligence in cardiovascular medicine. Curr Treat Options Cardiovasc Med 2019;21:25.
3. Casclang-Verzosa G, Shrestha S, Khalil MJ, et al. Network tomography for understanding phenotypic presentations in aortic stenosis. J Am Coll Cardiol Img 2019;12:236–48.
4. Tokodi M, Shrestha S, Bianco C, et al. Inter-patient similarities in cardiac function: a platform for personalized cardiovascular medicine. J Am Coll Cardiol Img 2020;13:1119–32.

**KEY WORDS** echocardiography, heart failure, machine learning
High-Resolution Late Gadolinium Enhancement Magnetic Resonance for the Diagnosis of Myocardial Infarction With Nonobstructed Coronary Arteries

Pierre-François Lintingre, MD,a Hubert Nivet, MD,a Stéphanie Clément-Guinaudeau, MD, MSc,a Claudia Camaioni, MD,a Soumaya Sridi, MD,a Olivier Corneloup, MD,a Edouard Gerbaud, MD,a Pierre Coste, MD,b Gael Dournes, MD, PhD,a Valérie Latrabe, MD,a François Laurent, MD,a c Michel Montaudon, MD, PhD,a c Hubert Cochet, MD, PhD,a c

ABSTRACT

OBJECTIVES The aim of this study was to assess the diagnostic yield of cardiac magnetic resonance (CMR) including high-resolution (HR) late gadolinium enhancement (LGE) imaging using a 3-dimensional respiratory-navigated method in patients with myocardial infarction with nonobstructed coronary arteries (MINOCA).

BACKGROUND CMR plays a pivotal role for the diagnosis of patients with MINOCA. However, the diagnosis remains inconclusive in a significant number of patients, the results of CMR being either negative or uncertain (i.e., compatible with multiple diagnoses).

METHODS Consecutive patients categorized as having MINOCA after blood testing, electrocardiography, coronary angiography, and echocardiography underwent conventional CMR, including cine, T2-weighted, first-pass perfusion, and conventional breath-held LGE imaging. HR LGE imaging using a free-breathing method allowing improved spatial resolution (voxel size 1.25 × 1.25 × 2.5 mm) was added to the protocol when the results of conventional CMR were inconclusive and was optional otherwise. Diagnoses retained after reviewing conventional CMR were compared with those retained after the addition of HR LGE imaging.

RESULTS From 2013 to 2016, 229 patients were included (mean age 56 ± 17 years, 45% women). HR LGE imaging was performed in 172 patients (75%). In this subpopulation, definite diagnoses were retained after conventional CMR in 86 patients (50%): infarction in 39 (23%), myocarditis in 32 (19%), takotsubo cardiomyopathy in 13 (8%), and other diagnoses in 2 (1%). In the remaining 86 patients (50%), results of CMR were inconclusive: negative in 54 (31%) and consistent with multiple diagnoses in 32 (19%). HR LGE imaging led to changes in final diagnosis in 45 patients (26%) and to a lower rate of inconclusive final diagnosis (29%) (p < 0.001). In particular, HR LGE imaging could reveal or ascertain the diagnosis of infarction in 14% and rule out the diagnosis of infarction in 12%. HR LGE imaging was particularly useful when the results of transthoracic echocardiography, ventriculography, and conventional CMR were negative, with a 48% rate of modified diagnosis in this subpopulation.

CONCLUSIONS HR LGE imaging has high diagnostic value in patients with MINOCA and inconclusive findings on conventional CMR. This has major diagnostic, prognostic, and therapeutic implications.

(J Am Coll Cardiol Img 2020;13:1135–48) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Patients with myocardial infarction with nonobstructed coronary arteries (MINOCA) represent a major diagnostic, prognostic, and therapeutic challenge in cardiology (1). Up to 5% to 10% of patients referred for coronary angiography for suspected myocardial infarction show no evidence of obstructive coronary artery disease (CAD) (2). The term “MINOCA” has been introduced as a “working diagnosis,” given the multiple underlying mechanisms that can lead to such presentation. These include ischemic injuries secondary to type 1 or type 2 acute myocardial infarction (3), as well as takotsubo cardiomyopathy and acute myocarditis. The clinical management and prognosis being highly different according to the underlying etiology, dedicated diagnostic work-up is recommended (1). In this context, cardiac magnetic resonance (CMR) plays a pivotal role (4). Among other methods, late gadolinium enhancement (LGE) imaging is critical, the final diagnosis being based largely on the detection and assessment of the transmural distribution of myocardial injuries (5). However, in a substantial number of patients, the underlying etiology remains uncertain after CMR, the results of which are either negative or compatible with multiple diagnoses (2,6,7). Because patients with negative results on CMR have lower troponin values (8,9), we hypothesized that a major limitation of CMR is its spatial resolution, insufficient to detect small areas of myonecrosis. Free-breathing LGE imaging was recently introduced for high-resolution (HR) imaging of the left atrial wall (10). It has also been shown valuable in providing a detailed 3-dimensional architecture of ventricular scars to guide catheter ablation for ventricular arrhythmia (11). Using this method, spatial resolution is improved, with voxel size decreased by 4-fold compared with conventional breath-held methods. The aim of the present study was to assess the diagnostic yield of CMR including HR LGE imaging in patients presenting with MINOCA.

METHODS

POPULATION AND STUDY DESIGN. From January 2013 to March 2016, consecutive patients referred to the University Hospital of Bordeaux for the management of MINOCA were prospectively recruited. The pre-inclusion diagnostic work-up comprised blood testing including cardiac troponin, C-reactive protein, and leukocyte count; electrocardiography; coronary angiography; and transthoracic echocardiography (TTE). Inclusion criteria were in line with the recent European Society of Cardiology position paper defining MINOCA (1): 1) criteria for acute myocardial infarction including troponin rise above the 99th percentile upper reference limit and corroborative clinical evidence of infarction according to the fourth universal definition of myocardial infarction (4); 2) absence of obstructive CAD ($\geq$50% stenosis) on coronary angiography; and 3) no clinically overt specific cause for the acute presentation. Patients diagnosed with clinically suspected myocarditis according to the European Society of Cardiology 2013 myocarditis task force (12) were not considered for inclusion. Exclusion criteria were contraindications to CMR, including patients with implantable cardioverter-defibrillators, and history of acute coronary syndrome associated with troponin rise. All patients underwent conventional CMR including LGE imaging using usual breath-held methods. Free-breathing HR LGE imaging was systematically added to the protocol in patients with inconclusive findings after conventional CMR and was optional otherwise, depending on the clinical work flow.

CMR ACQUISITION. Studies were performed on a 1.5-T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) equipped with a 32-channel cardiac coil. The protocol comprised cine, T2-weighted, and first-pass perfusion imaging, as well as conventional LGE imaging performed 10 min post-contrast using 2 breath-held methods in 3 stacks of contiguous slices encompassing the whole ventricles in short-axis, 2-chamber, and 4-chamber orientations. The first method was a 3-dimensional inversion recovery-prepared turbo fast low-angle shot sequence (voxel size 1.8 × 1.4 × 6 mm) and the second a 2-dimensional phase-sensitive inversion recovery sequence (pixel size 1.8 × 1.3 mm, thickness 6 mm). Conventional CMR findings were reviewed in real time during the CMR study by a single reader (15 years’ experience in CMR). Free-breathing HR LGE acquisition was performed using a free-breathing turbo inversion recovery-prepared fast low-angle shot technique with a voxel size of 1.8 × 1.4 × 6 mm.
imaging was systematically added to the protocol in patients with inconclusive findings after conventional CMR and was optional otherwise, depending on the clinical workflow. In patients eligible for HR LGE imaging, an additional inversion time scout scan was performed after conventional LGE imaging, hence 15 to 20 min after contrast injection. HR LGE imaging was then performed using a 3-dimensional, inversion recovery-prepared, electrocardiographically gated, respiration-navigated gradient-echo pulse sequence with fat saturation (voxel size 1.25 × 1.25 × 2.5 mm), acquisition time 8 to 12 min depending on heart rate and breath rate (9). Detailed protocols and sequence parameters are provided in the Supplemental Appendix.

**CMR Analysis and Interpretation.** CMR interpretation was performed retrospectively, after the completion of patient inclusion. Two readers (with 5 and 15 years’ experience in CMR) analyzed all conventional CMR studies in a random order. This interpretation was performed months or years after the CMR study, and the readers were blinded to the initial CMR report. Thus, the interpretation of conventional CMR images was truly blinded to the 3-dimensional HR LGE dataset, and the readers did not know whether HR LGE imaging had been subsequently performed. Then, the same readers analyzed again the entire population, this time adding HR LGE imaging to the conventional CMR analysis. In addition, a single reader (5 years’ experience) read all studies twice in a random order to document intraobserver agreement. Left ventricular volumes and ejection fraction were quantified using Argus software (Siemens Medical Systems). Ventricular dilatation and systolic dysfunction were defined on the basis of previously reported normal values (13). Cine images were visually assessed to look for left ventricular or right ventricular wall motion abnormalities and pericardial effusion. T2-weighted images were analyzed to look for myocardial edema. Perfusion imaging was reviewed to look for perfusion defects at rest. LGE imaging was analyzed to look for myocardial or pericardial LGE. Conventional LGE images were

---

**TABLE 1** Baseline Characteristics (N = 229)

| Parameter                                      | Value       |
|-----------------------------------------------|-------------|
| Age (yrs)                                     | 56 ± 17     |
| Female                                        | 104 (45)    |
| History of cardiac disorder                   | 21 (9)      |
| If so which diagnosis                         |             |
| Atrial fibrillation                            | 11 (6)      |
| Valvular heart disease                         | 4 (2)       |
| Treated ventricular septal defect              | 2 (1)       |
| Dilated cardiomyopathy                         | 1 (0.4)     |
| Left bundle branch block                       | 1 (0.4)     |
| Long-QT syndrome                               | 1 (0.4)     |
| Atrioventricular block                         | 1 (0.4)     |
| CAD risk factors                               |             |
| Hypertension                                   | 69 (30)     |
| Smoking                                        | 85 (37)     |
| Diabetes mellitus                              | 21 (9)      |
| Hyperlipidemia                                 | 65 (28)     |
| Overweight (BMI 25–29.9 kg/m²)                 | 107 (47)    |
| BMI (kg/m²)                                    | 25.7 ± 5.2  |
| Family history of premature CAD                | 35 (15)     |
| Clinical presentation                          |             |
| Typical angina                                 | 119 (52)    |
| Atypical chest pain                            | 101 (44)    |
| Pericarditis-like chest pain                   | 9 (4)       |
| Recent history of chest pain                   | 37 (16)     |
| Infection (within the preceding 30 days)       | 59 (26)     |
| Emotional stress                               | 17 (7)      |
| Dyspnea                                        | 30 (13)     |
| Palpitation                                    | 17 (7)      |
| Fever                                          | 7 (3)       |
| Light-headedness                               | 37 (16)     |
| Syncope                                        | 7 (3)       |
| Biological tests                               |             |
| Troponin (peak/normal)                         | 35 (10-120) |
| CRP (mg/l)                                     | 2.9 (0.2-23.0) |
| Elevated C-reactive protein (>5 mg/l)          | 95 (42)     |
| High leukocyte count                           | 70 (31)     |
| ECG at presentation                            |             |
| STEMI                                          | 85 (37)     |
| Sinus rhythm                                   | 222 (97)    |
| LBBB                                           | 8 (4)       |
| RBBB                                           | 10 (4)      |

**TABLE 1 Continued**

| Parameter                                      | Value       |
|-----------------------------------------------|-------------|
| Transthoracic echocardiography                 |             |
| LVEF (%)                                       | 57 ± 7      |
| Normal results                                 | 124 (54)    |
| Regional WMA                                   | 90 (39)     |
| Diffuse WMA                                     | 41 (18)     |
| Pericardial effusion                           | 6 (3)       |
| Other finding                                  | 6 (3)       |
| Coronary angiography                           |             |
| Radiographic angiography                        | 222 (97)    |
| Coronary CTA                                    | 7 (3)       |
| Normal coronary arteries                        | 125 (55)    |
| Non-obstructive CAD                            | 104 (45)    |
| Abnormal ventriculography*                     | 70 (40)     |

Values are mean ± SD, n (%), or median (interquartile range). *Data not available in 56 (24%) patients.

BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; CTA = computed tomographic angiography; ECG = electrocardiography; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; STEMI = ST-segment elevation myocardial infarction; TTE = transthoracic echocardiography; WMA = wall motion abnormality.
High-Resolution LGE CMR for the Diagnosis of MINOCA

Lintingre et al.

When the positivity of LGE imaging was uncertain, the extent of LGE was quantified in numbers of segments involved, using the 17-segment American Heart Association model. The criterion to diagnose myocardial infarction on CMR was the presence of definite subendocardial or transmural LGE (14). The criterion to diagnose myocarditis was the presence of definite midwall and/or subepicardial LGE in the absence of subendocardial LGE (15). The criterion to diagnose takotsubo cardiomyopathy was either: 1) a wall motion abnormality involving the entire apical or basal levels in the absence of myocardial LGE (14); or 2) a similar wall motion abnormality documented on pre-inclusion ventriculography or TTE in a patient with normal wall motion and negative LGE on CMR. Results of CMR were categorized as conclusive when patients fulfilled the criteria for a definite diagnosis and as inconclusive otherwise: negative or uncertain CMR findings (possible LGE or definite subendocardial or transmural LGE with an uncertain pattern, i.e., compatible with multiple diagnoses).

Each reader established a first diagnosis on the basis of non-CMR diagnostic tests and conventional CMR only, blinded to the 3-dimensional HR LGE imaging. Patients with HR LGE were analyzed a second time, only, blinded to the 3-dimensional HR LGE imaging.

**TABLE 2 Conventional CMR Findings in the Total Population (N = 229)**

| Chest pain to CMR delay (days) | 4 (2–8) |
|-------------------------------|---------|
| Extracardiac findings         |         |
| Pulmonary infiltrate          | 6 (3)   |
| Pleural effusion              | 9 (4)   |
| Cine imaging                  |         |
| Pericardial effusion          | 8 (4)   |
| RVEF impairment               | 1 (0.4) |
| LVEF (%)                      | 61 ± 9  |
| LVEF impairment               | 48 (21) |
| LVEDVi (ml/m²)                | 73 ± 18 |
| Regional WMA                  | 80 (35) |
| Rest perfusion*               |         |
| Perfusion defect              | 20 (13) |
| T2 imaging                    |         |
| Myocardial T2w abnormality    | 95 (41) |
| Conventional LGE findings     |         |
| Negative                      | 83 (36) |
| Definite myocardial LGE       | 129 (56) |
| Possible myocardial LGE       | 17 (7)  |
| Ischemic LGE pattern          | 61 (27) |
| Nonischemic LGE pattern       | 69 (30) |
| Uncertain LGE pattern         | 16 (7)  |
| Transmural LGE                | 30 (13) |
| LGE extent (number of segments)| 1 (0–2) |
| Pericardial LGE               | 3 (1)   |
| Post-conventional CMR diagnosis|      |
| Definite diagnoses            | 138 (60) |
| AM                            | 57 (25) |
| MI                            | 56 (24) |
| TT                            | 22 (10) |
| Other                         | 3 (1)   |
| Inconclusive diagnoses        | 91 (40) |
| Negative results on CMR       | 59 (26) |
| Either MI or AM               | 14 (6)  |
| Either MI or TT               | 2 (1)   |
| Either MI or negative         | 4 (2)   |
| Either AM or negative         | 12 (5)  |

Values are median (IQR), n (%), or mean ± SD. *Data not available in 76 (33%) patients.

AM = acute myocarditis; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; MI = myocardial infarction; RVEF = right ventricular ejection fraction; T2w = T2-weighted imaging; TT = takotsubo cardiomyopathy; other abbreviations as in Table 1.

**FOLLOW-UP.** Patients with a final diagnosis of takotsubo cardiomyopathy underwent follow-up imaging using CMR or TTE at 3 months. Subsequent outcomes were analyzed in the subset of the population that could be practically followed at our institution (follow-up at 3 months and then every year). In case of recurrent acute coronary syndrome, the diagnosis of the episode was compared with the diagnosis retained after the initial MINOCA episode.

**STATISTICAL ANALYSIS.** The Shapiro-Wilk test of normality was used to assess whether quantitative data conformed to the normal distribution. Continuous data are expressed as mean ± SD when following a normal distribution and as median (interquartile range) otherwise. Categorical data are expressed as fraction (percentage). Nonweighted Cohen’s kappa coefficients were used to analyze intra and interobserver agreement on the final diagnosis. Independent continuous variables were compared using independent-sample parametric (unpaired Student’s t-test).
t-test or analysis of variance) or nonparametric (Mann-Whitney U test or Kruskal-Wallis test) tests depending on data normality. When differences were found among groups by using analysis of variance (or the Kruskal-Wallis test), the multiple-comparisons Tukey-Kramer method (or the Conover-Iman test) was used to compare all pairs of groups. Dependent continuous variables were compared using paired-sample parametric or nonparametric tests (paired Student’s t-test, Wilcoxon signed rank test) depending on data normality. Independent categorical variables were compared using the chi-square test when expected frequencies were ≥5 and the Fisher exact test when they were <5. When a difference was found by testing multiple (>2) categorical samples, the Marascuillo procedure was used to compare all pairs of groups. Dependent categorical variables were compared using the paired-sample McNemar test. All statistical tests were 2-tailed. A p value <0.05 was considered to indicate statistical significance. Analyses were performed using NCSS 8 (NCSS Statistical Software, Kaysville, Utah).

RESULTS

POPULATION. A total of 229 patients presenting with MINOCA were recruited (mean age 56 ± 17 years, 45% women). The characteristics of the studied population are shown in Table 1. The median troponin increase was 35 times the upper limit of normal (interquartile range: 10 to 120 times). Electrocardiography showed ST-segment elevation myocardial infarction in 85 patients (37%). Results of TTE were negative in 124 patients (54%) and showed diffuse and regional wall motion abnormalities in 41 (18%) and 90 (39%), respectively. Coronary angiography showed normal arteries in 125 patients (55%) and nonobstructive CAD in 104 (45%). All patients underwent CMR including cine imaging, T2-weighted imaging, and LGE imaging using breath-held methods. First-pass perfusion imaging at rest was not available in 76 patients (33%). The delay between the onset of chest pain and the CMR study was 4 days (interquartile range: 2 to 8 days). Conventional CMR findings in the total population are listed in Table 2. Examples of definite diagnoses of acute myocardial infarction, acute myocarditis, and takotsubo cardiomyopathy are shown in Supplemental Figures 1 to 3, respectively.

POPULATION STUDIED WITH HR LGE IMAGING. HR LGE imaging was added to the protocol when the diagnosis remained inconclusive after conventional LGE imaging and was optional otherwise. A total of 5 patients with negative findings on conventional CMR did not complete HR LGE imaging, because of poor tolerance during CMR. In total, HR LGE imaging was performed in 172 patients (75%). The characteristics of patients with (n = 172) and without (n = 57) HR LGE are compared in Supplemental Table 1. The population with additional HR LGE imaging was, as expected, more likely to show uncertain diagnosis after conventional CMR (50% vs. 9%; p < 0.001). In addition, the troponin peak and the rate of elevated C-reactive protein were lower (p < 0.001 and p = 0.02, respectively), and results of TTE and ventriculography more frequently negative (p = 0.03 and p = 0.02, respectively).

CONVENTIONAL VERSUS HR LGE FINDINGS. After reviewing conventional CMR findings in this subpopulation (n = 172), definite diagnoses could be retained in 86 patients (50%), including myocardial infarction in 39 (23%), acute myocarditis in 32 (19%), takotsubo cardiomyopathy in 13 (8%), and other diagnoses in 2 (1%; hypertrophic cardiomyopathy and endomyocardial fibrosis). In the remaining 86 patients (50%), results of conventional CMR were inconclusive: negative in 54 (31%) and consistent with multiple diagnoses (infarction or myocarditis in 14 [8%], myocarditis or negative results in 12 [7%],

| TABLE 3 LGE Findings and Final Diagnosis Before and After HR LGE Imaging |
|-----------------------------------------------|-----------------|-----------------|------------------|
| LGE characteristics                          | Conventional LGE | Conventional and HR LGE | p Value |
| Negative myocardial LGE                      | 68 (39)          | 61 (35)          | 0.143 |
| Definite myocardial LGE                      | 87 (51)          | 110 (64)         | <0.001 |
| Possible myocardial LGE                      | 17 (10)          | 1 (1)            | <0.001 |
| Ischemic LGE pattern                         | 45 (26)          | 63 (37)          | <0.001 |
| Nonischemic LGE pattern                      | 44 (26)          | 47 (27)          | 0.629 |
| Uncertain LGE pattern                        | 15 (9)           | 1 (1)            | <0.001 |
| Transmural LGE                               | 17 (10)          | 19 (11)          | 0.754 |
| LGE extent (number of segments)              | 1 (0–2)          | 1 (0–2)          | 0.011 |
| Pericardial LGE                              | 3 (2)            | 5 (3)            | 0.625 |
| Post-CMR diagnosis                           |                 |                 |       |
| Definite diagnoses                           | 86 (50)          | 122 (71)         | <0.001 |
| AM                                            | 32 (19)          | 46 (27)          | 0.002 |
| MI                                            | 39 (23)          | 62 (36)          | <0.001 |
| TT                                            | 13 (8)           | 13 (8)           | 0.999 |
| Others                                        | 2 (1)            | 1 (1)            | 0.999 |
| Inconclusive diagnoses                       | 86 (50)          | 50 (29)          | <0.001 |
| Negative results on CMR                      | 54 (31)          | 48 (28)          | 0.211 |
| Either MI or AM                              | 14 (8)           | 1 (1)            | 0.001 |
| Either MI or TT                              | 2 (1)            | 0 (0)            | 0.480 |
| Either MI or negative                        | 4 (2)            | 0 (0)            | 0.134 |
| Either AM or negative                        | 12 (7)           | 1 (1)            | 0.003 |

Values are n (%) or median (interquartile range).
HR = high-resolution; other abbreviations as in Tables 1 and 2.
infarction or negative results in 4 [2%], and infarction or takotsubo cardiomyopathy in 2 [1%]). CMR results before and after reviewing HR LGE imaging are compared in Table 3. The rate of definite myocardial LGE was higher on HR LGE imaging than on conventional LGE (64% vs. 51%; p < 0.001). Likewise, the rate of uncertain LGE transmural location was lower on HR LGE imaging (1% vs. 15%; p < 0.001). Comparisons between conventional and HR LGE images are shown in Figure 1. The interpretation of myocardial injuries derived from HR LGE imaging led to a modification of the final diagnosis, either because of improved detection of myocardial injuries or because of improved assessment of LGE transmural location. Arrows indicate sites of LGE.

CHARACTERISTICS OF PATIENTS BENEFITING FROM HR LGE IMAGING. In a total of 40 patients, definite diagnoses were introduced after reviewing HR LGE images, while conventional CMR results were inconclusive or suggestive other diagnoses. The characteristics of these patients benefiting from HR LGE imaging are shown in the Central Illustration. Most diagnostic changes (41 of 45 [91%]) occurred in patients with inconclusive diagnoses after conventional CMR. After the addition of HR LGE imaging, the rate of inconclusive CMR decreased from 86 to 50 of 172 (50% vs. 29%; p < 0.001). Likewise, the number of patients with definite diagnoses of myocardial infarction and myocarditis increased (p < 0.001 and p = 0.002, respectively). In particular, the addition of HR LGE imaging could reveal or ascertain myocardial infarction in 24 patients (14%). In these patients, conventional CMR findings had been interpreted as negative in 4, compatible with multiple diagnoses in 17, and suggestive of different diagnoses in 3 (2 as definite myocarditis, and 1 as hypertrophic cardiomyopathy, in whom HR LGE imaging showed definite infarction). In addition, HR LGE imaging could rule out the diagnosis of myocardial infarction in 21 patients (12%). In these patients, conventional CMR findings had been interpreted as negative in 7, compatible with multiple diagnoses including infarction in 13, and as definitely suggestive of infarction in 1 (interpreted as definite myocarditis after HR LGE imaging).
The diagnoses retained after conventional cardiac magnetic resonance (CMR) methods and after the addition of HR LGE imaging are shown in the left and right columns, respectively. Connecting lines indicate diagnostic changes, the number of patients concerned being overlaid on each line. AM = acute myocarditis; HR = high-resolution; LGE = late gadolinium enhancement; MI = acute myocardial infarction; TT = takotsubo cardiomyopathy.

**CENTRAL ILLUSTRATION** Diagnostic Changes Introduced by HR LGE Imaging (172 Patients With Both Conventional CMR and HR LGE Imaging)

| CONVENTIONAL CMR | CMR WITH HR-LGE |
|------------------|-----------------|
| **Definite diagnoses** | **Definite diagnoses** |
| Definite AM N = 32 (19%) | Definite AM N = 46 (27%) |
| Definite TT N = 13 (8%) | Definite TT N = 13 (8%) |
| Others N = 2 (1%) | Others N = 1 (1%) |
| Definite MI N = 39 (23%) | Definite MI N = 62 (36%) |
| **Non-conclusive diagnoses** | **Non-conclusive diagnoses** |
| Negative CMR N = 54 (31%) | Negative CMR N = 48 (28%) |
| AM or MI N = 14 (8%) | AM or MI N = 1 (%) |
| MI or Negative N = 4 (2%) | MI or Negative N = 0 (0%) |
| MI or TT N = 2 (1%) | MI or TT N = 0 (0%) |
| AM or Negative N = 12 (7%) | AM or Negative N = 1 (1%) |

Lintingre, P.-F. et al. J Am Coll Cardiol Img. 2020;13(5):1135–48.

Imaging are analyzed in Table 4. They more frequently had negative findings on TTE, ventriculography, and cine magnetic resonance (p = 0.01, p = 0.02, and p = 0.04, respectively), and the pattern of hyperenhancement on conventional LGE imaging was more frequently uncertain (p < 0.001). The diagnosis after conventional CMR was more often negative or uncertain (p < 0.001) and less often consistent with myocarditis, infarction, or takotsubo cardiomyopathy (p = 0.01, p < 0.001, and p = 0.04, respectively). Examples of definite diagnoses introduced thanks to the addition of HR LGE imaging are shown in Figures 2 to 4.

**INTRA- AND INTEROBSERVER AGREEMENT ON FINAL DIAGNOSIS.** Agreement on final diagnosis after conventional CMR and after HR LGE imaging is listed in Table 5. Intra- and interobserver agreement on final diagnosis was excellent for both conventional CMR and HR LGE imaging. Intraobserver agreement was significantly higher than interobserver agreement (p < 0.05 for both conventional CMR and HR LGE imaging). Intraobserver and interobserver agreement was higher after HR LGE imaging than after conventional CMR methods only, although the difference was not statistically significant (p = NS).

**PATIENT CHARACTERISTICS ACCORDING TO FINAL DIAGNOSIS.** Including all available information and in the total population, the final diagnoses were myocarditis in 71 of 229 (31%), myocardial infarction in 79 of 229 (34%), takotsubo cardiomyopathy in 22 of 229 (10%), negative results on CMR in 53 of 229 (23%),
and uncertain results on CMR in 4 of 229 (2%). Patient characteristics according to final diagnosis are compared in Table 6.

**PATIENT OUTCOMES.** All 22 patients with definite diagnosis of takotsubo cardiomyopathy underwent follow-up imaging (CMR in 8, TTE in 14), revealing normalization of left ventricular wall motion in all cases. Clinical follow-up information could be retrieved for only 116 of 229 (51%), because other patients were not followed at our institution. The median follow-up duration was 2.9 years (interquartile range: 1.0 to 3.7 years). Adverse outcomes included rehospitalization in a cardiology department in 20 of 116 patients (17%), including 8 of 116 patients (7%) because of recurrence of acute coronary syndrome. In these 8 patients, initial diagnoses were infarction in 4, myocarditis in 3, and negative CMR findings in 1. These patients were also retained after recurrence, except for the patient with initial negative results on CMR, whose recurrence was attributed to myocardial infarction secondary to coronary vasospasm. Death occurred in 5 of 116 patients (4%), including 1 (1%) attributed to a cardiac cause (sudden cardiac arrest in a patient with initial diagnosis of myocardial infarction). The comparison of outcomes according to the final diagnosis retained after the initial MINOCA episode is shown in Table 7.

**DISCUSSION**

The present study is the first to introduce the use of free-breathing HR LGE imaging for the diagnostic work-up of MINOCA. Studying a series of 229 consecutive patients with MINOCA, including 172 using both conventional and free-breathing LGE methods, the results show that the addition of HR LGE imaging leads to a higher rate of definite myocardial LGE and a lower rate of LGE of uncertain transmural location. This translates into a change in final diagnosis in 26% of the patients undergoing both methods and a lower rate of inconclusive CMR. Most diagnostic changes occur in patients with negative or uncertain results on diagnostic work-up after TTE, ventriculography, and conventional CMR.

**POPULATION CHARACTERISTICS AND CONVENTIONAL CMR FINDINGS.** The inclusion criteria conformed to the definition of MINOCA (1). The demographics and risk factors of the population are consistent with prior large series of patients with MINOCA (2,16). Electrocardiographic findings are also consistent with prior reports on MINOCA, with <40% of patients exhibiting ST-segment elevation (2,17). Likewise, the rates of negative findings on TTE and nonobstructive CAD on angiography are in agreement with past studies (2,18,19). The conventional CMR protocol conformed to the guidelines of the Society for Cardiovascular Magnetic Resonance (20). The rate of negative findings on CMR and the distribution of etiologies in patients with positive CMR

---

**TABLE 4 Characteristics of Patients Benefiting From HR LGE Imaging**

| Diagnosis (n = 132) | Diagnosis (n = 40) | p Value |
|--------------------|--------------------|---------|
| Age (yrs)          | 57 ± 17            | 55 ± 17 | 0.503 |
| Female             | 64 (48)            | 19 (48) | 0.913 |
| History of cardiac disorder | 11 (8) | 4 (10) | 0.752 |
| Number of CAD risk factors | 1 (2-3) | 1 (2-3) | 0.600 |
| Clinical presentation |                       |         | |
| Typical angina     | 68 (52)            | 19 (48) | 0.656 |
| Atypical chest pain| 57 (43)            | 20 (50) | 0.447 |
| Pericarditis-like chest pain | 7 (5) | 1 (3) | 0.683 |
| Recent history of angina | 24 (18) | 6 (15) | 0.642 |
| Infection (within the preceding 30 days) | 27 (20) | 12 (30) | 0.207 |
| Emotional stress   | 12 (9)             | 1 (3)   | 0.304 |
| Dyspnea            | 16 (12)            | 4 (10)  | 0.999 |
| Palpitation        | 10 (8)             | 2 (5)   | 0.735 |
| Light-headedness or syncope | 25 (19) | 7 (18) | 0.838 |
| Laboratory findings |                       |         | |
| Troponin (peak/normal) | 27.3 (9.3–97.8) | 30.3 (8.4–59.2) | 0.080 |
| Elevated C-reactive protein (>5 mg/l) | 51 (39) | 13 (33) | 0.482 |
| High leukocyte count (>10 g/l) | 40 (30) | 11 (28) | 0.734 |
| ECG at presentation |                       |         | |
| STEMI              | 48 (36)            | 13 (33) | 0.655 |
| Sinus rhythm       | 129 (98)           | 40 (100)| 0.999 |
| LBBB or RBBB       | 9 (7)              | 3 (8)   | 0.999 |
| Transthoracic echocardiography |         |         | |
| LVEF (%)           | 57.0 ± 6.7         | 58.6 ± 5.6 | 0.169 |
| Normal TTE         | 70 (53)            | 30 (75) | 0.014 |
| Regional WMA       | 56 (42)            | 6 (15)  | 0.002 |
| Diffuse WMA        | 24 (18)            | 3 (8)   | 0.137 |
| Coronary angiography |                   |         | |
| Normal coronary arteries | 76 (58) | 23 (58) | 0.993 |
| Nonobstructive CAD  | 55 (42)            | 17 (42) | 0.993 |
| Abnormal ventriculography | 39 (41) | 6 (19) | 0.025 |
| Conventional CMR characteristics |         |         | |
| LVEF (%)           | 61.3 ± 9.2         | 64.0 ± 7.8 | 0.109 |
| Regional WMA       | 49 (37)            | 8 (20)  | 0.044 |
| Pericardial effusion| 6 (5)              | 1 (3)   | 0.999 |
| Myocardial T2w abnormality | 52 (39) | 14 (35) | 0.663 |
| Perfusion defect    | 12 (9)             | 3 (8)   | 0.999 |
| Negative myocardial LGE | 56 (42) | 12 (30) | 0.159 |
| Definite myocardial LGE | 70 (53) | 17 (42) | 0.242 |
| Possible myocardial LGE | 6 (5) | 11 (28) | <0.001 |
| Ischemic LGE pattern | 39 (30) | 6 (15) | 0.067 |
| Nonischemic LGE pattern | 36 (27) | 8 (20) | 0.356 |
| Uncertain LGE pattern | 1 (1) | 14 (35) | <0.001 |
| Transmural LGE     | 5 (4)              | 2 (5)   | 0.665 |
| LGE extent (number of segments) | 1 (0-2) | 1 (0-1) | 0.500 |
| Pericardial LGE    | 3 (2)              | 0 (0)   | 0.999 |

Continued on the next page
are consistent with past CMR series in patients with MINOCA (2,5,6,8,21,22). Regarding CMR methods, our results confirm that LGE is the cornerstone of the etiologic diagnosis in patients with MINOCA, while cine, T2-weighted, and first-pass perfusion imaging often produce negative results. The limited sensitivity of T2 imaging in the present study may be explained by incomplete cardiac coverage or by the intrinsic limitations of T2-weighted imaging for the assessment of myocardial edema. The negative results on T2 and cine imaging may also be explained by the delay between the onset of chest pain and the CMR study. Most patients were studied within the first week, but myocardial edema is known to show dynamic changes over that period (23,24). Likewise, transient wall motion abnormalities secondary to ischemic myocardial stunning or stress-induced cardiomyopathy may last only a few days, and cine imaging performed several days after the episode may be less sensitive than TTE performed on day 1.

This appeared to be quite common in our series, as 34% of the patients with negative CMR findings showed wall motion abnormalities on TTE at admission.

| TABLE 4 Continued | HR LGE Imaging Does Not Introduce a New Definite Diagnosis (n = 132) | HR LGE Imaging Introduces a New Definite Diagnosis (n = 40) | p Value |
|--------------------|---------------------------------------------------------------|-------------------------------------------------|-------|
| Conventional CMR diagnosis | | | |
| Negative or inconclusive results on CMR | 50 (38) | 36 (90) | <0.001 |
| Definite myocarditis | 30 (23) | 2 (5) | 0.010 |
| Definite myocardial infarction | 38 (29) | 1 (3) | <0.001 |
| Definite takotsubo cardiomyopathy | 13 (10) | 0 (0) | 0.041 |
| Other | 1 (1) | 1 (3) | 0.412 |

Values are mean ± SD, n (%), or median (IQR). *Refers to patients with definite diagnoses introduced after reviewing HR LGE images while conventional CMR results were normal, inconclusive, or suggestive of another diagnosis.

Abbreviations as in Tables 1 to 3.

**FIGURE 2** A 33-Year-Old Woman Benefiting From HR LGE Imaging

The patient presented with typical angina and mild troponin rise. Results of electrocardiography, transthoracic echocardiography, and coronary angiography were normal. On cardiac magnetic resonance on day 2, results of cine (end-diastole [A] and end-systole [B]), T2-weighted [C], first-pass rest perfusion [D], and conventional LGE [E,F] imaging were considered negative. HR LGE showed focal subendocardial enhancement on the inferolateral mid segment, consistent with microinfarction (arrows in G and H). Additional diagnostic work-up revealed no overt embolic cause on 24-h Holter monitoring, no biological substrate for thrombophilia, and no evidence of systemic vasculitis. Abbreviations as in Figure 1.
In line with prior studies, we found high rates of negative or uncertain findings after conventional CMR methods (2). Compared with conventional breath-held LGE methods, the amount of myocardium contained in each single voxel is decreased by 4-fold using HR LGE imaging (from 15.1 to 3.9 mm³). The addition of HR LGE imaging led to a higher rate of definite myocardial LGE and a lower rate of LGE of uncertain transmural location. The detection of LGE and the accurate description of its transmural distribution are major determinants of CMR diagnosis (6,14) and are often a complex interpretation. When LGE is focally transmural, it may be difficult to distinguish between a subendocardial and a subepicardial primary location of the injury. Likewise, small subendocardial injuries may be missed because of poor contrast with the blood pool, while those adjacent to trabeculations or papillary muscles may be misinterpreted as of intramural location (25). Last, subepicardial LGE may be mistaken for epicardial fat or coronary vessels. The addition of HR LGE imaging translated into a change in final diagnosis in 26% of the patients undergoing both methods and a lower rate of inconclusive CMR. Of note, most diagnostic changes introduced by HR LGE imaging were due to improved diagnostic confidence rather than to the detection of new myocardial lesions undetected by conventional LGE imaging (two-thirds vs. one-third) (Central Illustration).

This highlights the practical challenge of LGE interpretation in the context of MINOCA, in which myocardial injuries are smaller. Our results show that resolving these uncertainties has a significant impact on patient management. Particularly, HR LGE imaging could reveal or ascertain myocardial infarction in 14% and rule out myocardial infarction in 12%. Most diagnostic changes occurred in patients with inconclusive
diagnosis after TTE, ventriculography, and conventional CMR. The rate of modified diagnosis was 41 of 86 (48%) in this subpopulation compared with 4 of 86 (5%) in those with definite diagnoses retained after conventional CMR methods. Thus, the implementation of HR LGE imaging in clinical practice should focus on these patients.

The patient presented with atypical chest pain and mild troponin increase. Results of electrocardiography, transthoracic echocardiography, coronary angiography, and ventriculography were normal. On cardiac magnetic resonance performed on day 5, results of cine, T2-weighted (A), and rest perfusion (B) imaging were negative. On conventional LGE imaging, a focal enhancement was suspected on the inferomid segment, although categorized as uncertain (C,D). HR LGE imaging showed definite subendocardial enhancement consistent with infarction (E,F). Additional diagnostic work-up revealed no overt cause of myocardial infarction. Abbreviations as in Figure 1.

| TABLE 5 Intraobserver and Interobserver Agreement on Final Diagnosis |
|---------------------------------------------------------------|
| | Low-Resolution LGE Imaging | High-Resolution LGE Imaging |
| | (n = 229) | 95% CI | (n = 172) | 95% CI |
| Intraobserver agreement | κ = 0.978 | 0.953-1.000 | κ = 0.992 | 0.976-1.000 |
| Interobserver agreement | κ = 0.803 | 0.735-0.871 | κ = 0.903 | 0.850-0.956 |

CI = confidence interval; LGE = late gadolinium enhancement.
| Characteristics According to Final CMR Diagnosis | Negative CMR Results (n = 53) | Myocarditis (n = 71) | Myocardial Infarction (n = 79) | Takotsubo Cardiomyopathy (n = 22) | p Value |
|------------------------------------------------|-------------------------------|---------------------|-------------------------------|----------------------------------|--------|
| Age (yrs)                                      | 56 ± 16                       | 48 ± 15             | 57 ± 17                       | 72 ± 14                          | <0.001*†‡§ |
| Female                                         | 54.7                          | 28.2                | 40.5                          | 90.9                             | <0.001*†‡§ |
| History of cardiac disorder                    | 11.3                          | 2.8                 | 11.4                          | 13.6                             | 0.096  |
| Number of CAD risk factors                     | 2 (1–3)                       | 2 (1–3)             | 2 (1–3)                       | 3 (2–3)                          | 0.037* |
| Clinical presentation                          |                               |                     |                               |                                  |        |
| Typical angina                                 | 39.6                          | 50.7                | 67.1                          | 31.8                             | 0.003* |
| Atypical chest pain                            | 54.7                          | 43.7                | 31.7                          | 63.6                             | 0.013* |
| Pericarditis-like chest pain                   | 5.7                           | 5.6                 | 1.3                           | 4.6                              | 0.371  |
| Recent history of angina                       | 18.9                          | 18.3                | 16.5                          | 0.0                              | 0.124  |
| Infection (within the preceding 30 days)       | 20.80                         | 45.1                | 17.8                          | 4.6                              | <0.001* |
| Emotional stress                               | 5.7                           | 2.8                 | 3.8                           | 40.9                             | <0.001* |
| Dyspnea                                       | 18.9                          | 11.3                | 7.6                           | 22.7                             | 0.124  |
| Palpitation                                    | 9.4                           | 5.6                 | 5.1                           | 18.2                             | 0.179  |
| Light-headedness or syncope                    | 18.9                          | 14.1                | 12.7                          | 63.7                             | 0.001* |
| Laboratory findings                            |                               |                     |                               |                                  |        |
| Troponin (peak/normal)                         | 9.0 (4.8–18.0)                | 68.6 (20.0–212.8)   | 62.5 (18.0–141.7)             | 38.6 (24.6–75.5)                 | <0.001* |
| C-reactive protein value (mg/l)                | 12.4 ± 31.6                   | 34.0 ± 45.9         | 13.1 ± 33.2                   | 20.4 ± 31.3                      | <0.001* |
| Elevated C-reactive protein (>5 mg/l)          | 26.4                          | 63.4                | 29.1                          | 45.5                             | <0.001* |
| High leukocyte count (>10 g/l)                 | 24.5                          | 36.6                | 20.3                          | 59.1                             | 0.002* |
| ECG at presentation                            |                               |                     |                               |                                  |        |
| STEMI                                          | 18.9                          | 38.0                | 43.0                          | 59.1                             | 0.004* |
| Sinus rhythm                                   | 94.3                          | 98.6                | 98.7                          | 95.5                             | 0.368  |
| Arrhythmia                                     | 5.7                           | 1.4                 | 1.3                           | 4.6                              | 0.368  |
| LBBB or RBBB                                   | 7.6                           | 2.8                 | 10.1                          | 9.1                              | 0.349  |
| Transthoracic echocardiography                 |                               |                     |                               |                                  |        |
| LVEF (%)                                       | 57.5 ± 6.0                    | 58.9 ± 4.5          | 57.9 ± 6.3                    | 46.7 ± 8.5                       | <0.001* |
| Normal                                         | 66.0                          | 59.2                | 57.0                          | 4.6                              | <0.001* |
| Regional WMA                                   | 28.3                          | 32.4                | 36.7                          | 95.5                             | <0.001* |
| Diffuse WMA                                    | 17.0                          | 7.0                 | 11.4                          | 77.3                             | <0.001* |
| Coronary angiography                           |                               |                     |                               |                                  |        |
| Radiographic angiography                       | 94.3                          | 94.4                | 100.0                         | 100.0                            | 0.117  |
| Coronary CTA                                   | 5.7                           | 5.6                 | 0.0                           | 0.0                              | 0.117  |
| Normal coronary arteries                       | 58.5                          | 59.1                | 50.6                          | 40.9                             | 0.382  |
| Nonobstructive CAD                             | 41.5                          | 40.9                | 49.4                          | 59.1                             | 0.382  |
| Abnormal ventriculography                      | 0                             | 36                  | 40                            | 95                               | <0.001* |
| CMR characteristics                            |                               |                     |                               |                                  |        |
| LVEF (%)                                       | 65.1 ± 8.1                    | 60.9 ± 7.8          | 60.6 ± 8.5                    | 53.6 ± 13.4                      | <0.001* |
| Regional WMA                                   | 0                             | 22.5                | 58.2                          | 63.6                             | <0.001*†‡§ |
| Pericardial effusion                           | 5.7                           | 1.4                 | 2.5                           | 9.1                              | 0.199  |
| Myocardial T2w abnormality                     | 0                             | 42.3                | 62.0                          | 68.0                             | <0.001* |
| Perfusion defect                               | 0                             | 0                   | 25                            | 0                                | <0.001* |
| HR LGE imaging available                       | 84.9                          | 64.8                | 78.5                          | 59.1                             | 0.021* |
| Definite myocardial LGE                       | 0                             | 100                 | 100                           | 0                                | <0.001* |
| Possible myocardial LGE                       | 0                             | 0                   | 0                             | NA                               |        |
| Uncertain LGE pattern                          | 0                             | 0                   | 0                             | NA                               |        |
| Transmural LGE                                 | 0                             | 0                   | 27.8                          | 0                                | <0.001* |
| LGE extent (number of segments)                | 0 (0–0)                       | 2 (1–3)             | 1 (1–3)                       | 0 (0–0)                          | <0.001* |
| Pericardial LGE                                | 3.8                           | 2.8                 | 0                             | 0                                | 0.277  |

Values are mean ± SD, %, or median (interquartile range). *Statistical significance between negative CMR results and myocarditis. †Statistical significance between myocarditis and myocardial infarction. ‡Statistical significance between negative CMR results and takotsubo cardiomyopathy. §Statistical significance between myocarditis and takotsubo cardiomyopathy. ¶Statistical significance between myocardial infarction and takotsubo cardiomyopathy. **Statistical significance between negative CMR results and myocardial infarction. #Data not available in 16 (30%), 21 (30%), 17 (22%), and 1 (5%) patient, respectively. **Data not available in 14 (26%), 28 (39%), 25 (32%), and 7 (32%) patients, respectively. Abbreviations as in Tables 1 to 3.
CLINICAL IMPLICATIONS. The management of patients with MINOCA and uncertain diagnosis is a major dilemma in clinical cardiology. In these, myocardial infarction has not been ruled out or ascertained, and therapeutic management remains empirical or based on observational nonrandomized studies (26,27). A variety of methods have been proposed to detect occult causes of infarction, including imaging the coronary wall with intravascular ultrasound (28) or optical coherence tomography (29) or identifying a biological substrate for thrombophilia (30). The present study suggests that increasing the spatial resolution of CMR may also be instrumental in retaining or excluding the diagnosis of myocardial infarction, with major implications for patient management. Given that most cardiac magnetic resonance vendors have free-breathing LGE solutions available, our study supports the systematic integration of the method in patients undergoing CMR in the context of MINOCA, particularly when conventional CMR results are inconclusive. Applying such strategy would lead to a prolongation of the CMR study of about 10 min in about 40% of the patients, which in our opinion is acceptable.

STUDY LIMITATIONS. A main limitation was the absence of follow-up data in part of our population. Unfortunately, standardized follow-up was not practical in patients managed outside our institution. Another limitation was the absence of HR LGE imaging in 25% of the patients. For practical reasons, a prolongation of the CMR study in every patient was not compatible with our clinical work flow. However, HR LGE imaging was systematically performed when conventional CMR methods were inconclusive, which is the population benefiting the most from HR LGE imaging. HR LGE imaging was also performed in a sufficient number of patients with conclusive conventional CMR to conclude that the method is less valuable in this population. Last, because T1 and T2 mapping methods (31) were not locally available when the study was initiated, the incremental diagnostic value of HR LGE imaging in comparison with a CMR protocol including these sequences has not been evaluated.

CONCLUSIONS

In patients with MINOCA, the addition of HR LGE imaging using a free-breathing method improves the detection and assessment of the transmural distribution of myocardial injuries. This translates into changes in final diagnosis in about one-half of the patients with inconclusive findings after conventional CMR methods. In particular, HR LGE imaging can ascertain or rule out the diagnosis of myocardial infarction in a significant number of patients. These results have major implications for the management of patients with MINOCA.

ADDRESS FOR CORRESPONDENCE: Prof. Hubert Cochet, Unité d’Imagerie Thoracique et Cardiovasculaire, Hôpital Cardiologique du Haut-Lévêque, Avenue de Magellan, 33604 Bordeaux-Pessac, France.
E-mail: hcochet@wanadoo.fr.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Improving the spatial resolution of LGE imaging leads to a lower rate of noncontributory CMR in patients with MINOCA.

TRANSLATIONAL OUTLOOK: Future research should aim at developing LGE CMR methods with higher spatial resolution and acceptable acquisition times to be implemented as part of standard care for the diagnostic management of patients with MINOCA.
REFERENCES

1. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2017;38:143–53.

2. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015;131:861–70.

3. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138:e635–88.

4. Pathik B, Raman B, Mohd Amin NH, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2016;17:1466–52.

5. Torvill P, Gerbad E, Behagel A, et al. Myocarditis or “true” infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: a meta-analysis of individual patient data. Atherosclerosis 2015;241:87–91.

6. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of cardiac MRI and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. J Am Coll Cardiol Img 2019;12:1973–82.

7. Dastidar AG, Rodrigues JCL, Johnson TW, et al. Myocardial infarction with nonobstructed coronary arteries. J Am Coll Cardiol Img 2017;10:1204–6.

8. Gerbad E, Harcut E, Coste P, et al. Cardiac resonance imaging for the diagnosis of patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. Int J Cardiovasc Imaging 2012;28:783–94.

9. Christiansen JP, Edwards C, Sinclair T, et al. Detection of myocardial scar by contrast-enhanced cardiac resonance imaging in patients with troponin-positive chest pain and minimal angiographic coronary artery disease. Am J Cardiol 2006;97:678–81.

10. Oakes RS, Badger TJ, Khomolovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation 2009;119:1758–67.

11. Yamashita S, Sacher F, Mahida S, et al. Image integration to guide catheter ablation in scar-related ventricular tachycardia. J Cardiovasc Electrophysiol 2016;27:699–708.

12. Caffer ALP, Pankweut S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48.

13. Kawai-Boehm N, Maceira A, Valtsangiacomo-Buechel ER, et al. Normal values for cardiovascular magnetic resonance in adults and children. J Cardiovasc Magn Reson 2015;17:29.

14. Rajai P, Desai MY, Kwon D, Flamm SD. MR imaging of myocardial infarction. Radiographics 2013;33:1383–412.

15. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. J Am Coll Cardiol 2009;53:1475–87.

16. Daniel M, Ekenbäck C, Agewall S, et al. Risk factors and markers for acute myocardial infarction with angiographically normal coronary arteries. Am J Cardiol 2015;116:838–44.

17. Rossi R, Capodanno D, Lettieri C, et al. Long-term outcomes of patients with acute coronary syndrome and nonobstructive coronary artery disease. Am J Cardiol 2013;112:150–5.

18. Agewall S, Daniel M, Eurenius L, et al. Risk factors for myocardial infarction with normal coronary arteries and myocarditis compared with myocardial infarction with coronary artery stenosis. Angiology 2012;63:500–3.

19. Larsen AI, Galbraith PD, Glahi WA, Norris CM, Graham MM, Knudtson ML. Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries. Am J Cardiol 2005;95:261–3.

20. Kramer CM, Barkhausen J, Flamm SD, et al. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson 2013;15:91.

21. Collete O, Sorensen P, Frick M, et al. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. J Intern Med 2013;273:189–96.

22. Assoumou RG, Lyne JC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. Eur Heart J 2007;28:1242–9.

23. Abdel-Aty H, Cocker M, Meek C, Tyberg JV, Friedrich MG. Edema as a very early marker for acute myocardial ischemia. J Am Coll Cardiol 2009;53:1194–201.

24. Wright J, Adriaenssens T, Dymarkowski S, Desmet W, Bogaert J. Quantification of myocardial area at risk with t2-weighted CMR. J Am Coll Cardiol Img 2009;2:825–31.

25. Peters DC, Appelbaum EA, Nezafat R, et al. Left ventricular infarct size, peri-infarct zone, and papillary scar measurements: a comparison of high-resolution 3D and conventional 2D late gadolinium enhancement cardiac MR. J Magn Reson Imaging 2009;30:794–800.

26. Poku N, Noble S. Myocardial infarction with non obstructive coronary arteries (MINOCA): a whole new ball game. Expert Rev Cardiovasc Ther 2017;15:7–14.

27. Lindahl B, Baron T, Erlinge D, et al. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. Clinical perspective. Circulation 2017;135:1481–9.

28. Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation 2011;124:1414–25.

29. Jia H, Abthahan F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol 2013;62:1748–59.

30. Van de Water NS, French JK, Lund M, Hyde TA, White HD, Browett PJ. Prevalence of factor V Leiden and prothrombin variant G20210A in patients age >50 years with no significant stenoses at angiography three to four weeks after myocardial infarction. J Am Coll Cardiol 2000;36:717–22.

31. Ugander M, Bagi PS, Oki AJ, et al. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. J Am Coll Cardiol Img 2012;5:596–603.

KEY WORDS: cardiac magnetic resonance, late gadolinium enhancement, myocardial infarction with nonobstructed coronary arteries.

APPENDIX
For the CMR protocol and pulse sequence parameters and supplemental figures and a table, please see the online version of this paper.
EDITORIAL COMMENT

Value of Late Gadolinium Enhancement Imaging in Diagnosis of Myocardial Infarction and Unobstructed Coronary Arteries*

Raymond Y. Kwong, MD, MPH,a Afshin Farzaneh-Far, MD, PhDb,c

Until recently, patients who presented with myocardial infarction and unobstructed coronary arteries (MINOCAs) were a diagnostic and therapeutic mystery. Optimal management of these patients was unclear because the underlying cause(s) remained undefined using routine testing with electrocardiography, troponin levels, echocardiography, and even invasive coronary angiography. MINOCAs are neither uncommon nor benign (1,2). These patients represent up to 10% of those presenting with myocardial infarction—an proportion that may well increase with routine adoption of high-sensitivity troponin assays (3). Moreover, all-cause mortality in these patients has been reported to be as high as 4.7% at 1 year (3). Another study reported that patients with MINOCAs experience a similar rate of major adverse cardiac events at 12 months as that of patients with 1- or 2-vessel obstructive coronary artery disease who present with an acute myocardial infarction (4).

Over the last few years, many studies have demonstrated the usefulness of cardiovascular magnetic resonance (CMR) in providing an underlying diagnosis in patients with MINOCAs. CMR in this clinical setting is now incorporated into recommendations by professional societies, such as the European Society of Cardiology (5). CMR can provide detailed information on cardiac structure, function, and tissue characterization. In particular, visualization of myocardial scar by late gadolinium enhancement (LGE) has proven pivotal in diagnosing the underlying causes of MINOCAs. The basic principle underlying the LGE pulse sequence is inversion recovery imaging after a 5- to 10-min delay following intravenous administration of gadolinium contrast (6,7). Signal intensity from the normal myocardium is specifically suppressed by the inversion recovery preparation pulse, so that normal myocardium appears nulled or black, whereas nonviable regions that contain myocardium with ruptured cell membranes and a high concentration of gadolinium contrast appear bright or enhanced. In general, LGE lesions in patients with MINOCAs are small, and a variety of pulse sequences have been developed over the years to sensitively capture the pattern and presence of LGE (8). These include: 1) typical segmented 2-dimensional (2D) breath-held pulse sequences (9) with or without phase-sensitive inversion recovery (PSIR) (10); 2) single-shot, 2D sequences with or without PSIR that are acquired within 1 heartbeat and do not require a breath-hold (11); 3) segmented 3D sequences that are acquired with a breath-hold; or 4) segmented 3D sequences that are acquired free-breathing using a respiratory navigator capable of acquiring high in-plane spatial resolution (12). Each of these pulse sequences are based on compromise in certain imaging parameters that may have some advantages (and disadvantages), depending on the clinical situation. The 3D respiratory-
navigated sequence typically requires a 10 to 15 min acquisition with the patient breathing normally. Although it can provide higher spatial resolution with isotropic voxels, it is dependent on regular rate and depth of breathing and can be adversely affected by arrhythmias. Therefore, it has not been widely used in most clinical CMR laboratories.

In this issue of JACC, Lintingre et al. (13) examined the diagnostic impact of adding a high-resolution 3D respiratory-navigated LGE sequence—which they refer to as high resolution (HR) LGE—to a standard CMR protocol in a subset of patients with MINOCAs at a single center. This retrospective study included 229 patients with a diagnosis of MINOCAs. In 172 of these patients, HR-LGE was added to the end of a standard CMR protocol (cine, T2 weighted, resting perfusion, and conventional LGE). This was a nonrandom subset with the HR-LGE imaging acquisition added to the standard CMR protocol when either an experienced CMR reader believed that the standard LGE findings were inconclusive at the time of the CMR or as an optional extra sequence. In this subset of patients who underwent both standard and HR-LGE, the investigators blindly read the studies and examined the value of additional HR-LGE in reducing the number of inconclusive studies. Inconclusive studies were defined as those that were either normal or consistent with multiple diagnoses. They found that 50% of patients had inconclusive studies after standard LGE imaging, which was reduced to 29% with HR-LGE. They also noted that addition of HR-LGE led to a change in diagnosis in 26% of patients, based on diagnosing or excluding myocardial infarction.

Of the total population of 229 patients, 91 were categorized as inconclusive after standard LGE imaging (i.e., a conclusive diagnosis was made in only 60% of patients). Interestingly, diagnostic yield in recent previous studies that used conventional 2D LGE ranged from 74% (CMR performed at 37 days) to 87% (CMR performed at 6 days) (14,15). Thus, diagnostic yield using conventional LGE in the current study appeared to be significantly lower than that in some studies in the medical literature in this setting. This is despite CMR imaging being performed early, within 2 to 8 days of chest pain (median: 4 days).

It is also important to realize that the HR-LGE sequence requires a longer scanning time; image quality can be limited by patient movement or in those with irregular depth and rate of breathing, as well as arrhythmias. This factor may have introduced a selection bias in obtaining the additional HR-LGE sequence, that is, more cooperative patients without arrhythmias who tolerated additional time in the scanner were more likely to have been selected. Thus, whether these findings would apply to all patients, or at least currently, if HR-LGE can serve as a practical replacement of the conventional LGE method, is unclear. In addition, HR-LGE imaging was performed later than the regular 2D-LGE sequence, by which time the blood pool signal was significantly less bright, which likely allowed better delineation of subendocardial LGE (i.e., myocardial infarction). The investigators clearly showed that the primary change in diagnosis, with addition of the HR-LGE sequence, was related to ruling in or excluding myocardial infarction. The difficulty in discerning subendocardial LGE from the blood pool signal can have a significant impact on diagnostic certainty in MINOCAs. In this context, the recent development of black-blood LGE sequences that suppress the blood pool signal will be of great interest (16,17).

Lintingre et al. (13) are to be congratulated for the significant value of CMR in diagnosing the underlying causes of MINOCAs, adding to the growing literature. Their finding that HR-LGE imaging is associated with significant diagnostic gains may lead to improvements in therapeutic decision-making. This work builds on the original technical development of this pulse sequence by Peters et al. (12) and provides clinical evidence for use of HR-LGE in a common clinical scenario. It is important to emphasize that MINOCA should not be a final diagnosis and that identification of the underlying etiology is critical. In this regard, Lintingre et al. (13) provide further evidence that CMR should play a pivotal role in the workup of these patients. Although CMR can provide improved diagnosis of the underlying causes of MINOCA, the optimal therapeutic strategies in these patients needs further exploration with prospective randomized studies (18). Because of the growing data on the diagnostic role of CMR in MINOCA, there is now sufficient evidence for consideration of outcome-based clinical trials to evaluate the value of CMR-guided management in these patients compared with a traditional empirical approach.

ADDRESS FOR CORRESPONDENCE: Dr. Raymond Y. Kwong, Cardiovascular Division, Department of Medicine, Brigham & Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: rykwong@bwh.harvard.edu.
REFERENCES

1. Dreyer RP, Tavella R, Curtis JP, et al. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. Eur Heart J 2019 Jun 21 [E-pub ahead of print].

2. Barr PR, Harrison W, Smyth D, Flynn C, Lee M, Kerr AJ. Myocardial infarction without obstructive coronary artery disease is not a benign condition (ANZACS-QI 10). Heart Lung Circ 2018;27:165–74.

3. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and non-obstructive coronary arteries. Circulation 2015;131:861–70.

4. Kang WY, Jeong MH, Ahn YK, et al. Are patients with angiographically near-normal coronary arteries who present as acute myocardial infarction actually safe? Int J Cardiol 2011;146:207–12.

5. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2017;38:143–53.

6. Kwong RY, Farzaneh-Far A. Measuring myocardial scar by CMR. J Am Coll Cardiol Imag 2011;4:157–60.

7. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992–2002.

8. Kim RJ, Shah DJ, Judd RM. How we perform delayed enhancement imaging. J Cardiovasc Magn Reson 2003;5:505–14.

9. Simonetti OP, Kim RJ, Fieno DS, et al. An improved MR imaging technique for the visualization of myocardial infarction. Radiology 2001;218:215–23.

10. Kellman P, Arai AE, McVeigh ER, Aletras AH. Phase-sensitive inversion recovery for detecting myocardial infarction using gadolinium-delayed hyperenhancement. Magn Reson Med 2002;47:372–83.

11. Sievers B, Elliott MD, Hurwitz LM, et al. Rapid detection of myocardial infarction by subsecond, free-breathing delayed contrast-enhancement cardiovascular magnetic resonance. Circulation 2007;115:236–44.

12. Peters DC, Appelbaum EA, Nezafat R, et al. Left ventricular infarct size, peri-infarct zone, and papillary scar measurements: a comparison of high-resolution 3D and conventional 2D late gadolinium enhancement cardiac MR. J Magn Reson Imaging 2009;30:794–800.

13. Lintingre P-F, Nivet H, Clement-Guinaudeau S, et al. High-resolution late gadolinium enhancement magnetic resonance for the diagnosis of myocardial infarction with nonobstructed coronary arteries. J Am Coll Cardiol Imag 2020;13:1135–48.

14. Pathik B, Raman B, Mohd Amin NH, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2016;17:1146–52.

15. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. J Am Coll Cardiol Imag 2019;12:1973–82.

16. Kellman P, Xue H, Olivieri LJ, et al. Dark blood late enhancement imaging. J Cardiovasc Magn Reson 2016;18:77.

17. Kim HW, Rehwald WG, Jenista ER, et al. Dark-blood delayed enhancement cardiac magnetic resonance of myocardial infarction. J Am Coll Cardiol Imag 2018;11:1758–69.

18. Lindahl B, Baron T, Erlinge D, et al. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. Circulation 2017;135:1481–9.

KEY WORDS cardiac magnetic resonance imaging, cardiomyopathy, late gadolinium enhancement, myocardial infarction, myocardial infarction with nonobstructed myocarditis
Stress-Only Adenosine CMR Improves Diagnostic Yield in Stable Symptomatic Patients With Coronary Artery Calcium

Dorine Rijlaarsdam-Hermsen, MD,a,b,c Mallory Lo-Kioeng-Shioe, BSc,c Ron T. van Domburg, PhD,c Jaap W. Deckers, MD, PhD,a Dirkjan Kuijpers, MD, PhD,b Paul R.M. van Dijkman, MD, PhDa

ABSTRACT

OBJECTIVES This study assessed whether adenosine stress-only perfusion cardiac magnetic resonance (CMR) following a positive coronary artery calcium (CAC) score improved the diagnostic yield of invasive coronary angiography (CAG) in patients with stable chest pain. The study also established the association between positive CAC scores and stress-induced myocardial ischemia.

BACKGROUND The diagnostic yield of catheterization among patients with suspected coronary artery disease (CAD) is low. Improved patient selection and diagnostic testing are necessary. The CAC score can minimize unnecessary diagnostic testing, and in low-risk patients, normal CMR results have a high negative predictive value. Less comprehensive protocols may be sufficient to guide further work-up.

METHODS A total of 642 consecutive patients (mean age: 63 years; 50% women) with stable chest pain and CAC scores of >0 who were referred for CMR were enrolled. Patients with a perfusion defect were subsequently examined by CAG. Patients were followed up for 1 year. Outcome was obstructive CAD.

RESULTS Obstructive CAD was present in 12% of patients. For CAD diagnosis, the sensitivity of adenosine CMR was 90.9% (95% confidence interval [CI]: 88.7 to 93.1), specificity was 98.7% (95% CI: 97.9 to 99.6), positive predictive value was 92.0% (95% CI: 89.8 to 94.1), and negative predictive value was 98.6% (95% CI: 97.6 to 99.5). A CAC score between 0.1 and 100 without typical angina was associated with obstructive CAD in only 3% of patients. Patients with nonanginal chest pain and a CAC score ≥400 had obstructive CAD (16%).

CONCLUSIONS Stress-only adenosine CMR had high diagnostic accuracy and served as an efficient gatekeeper to CAG in stable patients with a CAC score >0. Patients with CAC scores between 0.1 and 100 could be deferred from further testing in the absence of clinical features that suggested high risk. However, in patients with CAC score ≥400, functional testing should be indicated, regardless of the type of chest pain. (J Am Coll Cardiol Img 2020;13:1152–60) © 2020 by the American College of Cardiology Foundation.

Conventional coronary angiography (CAG) remains the reference standard for the diagnosis of obstructive coronary artery disease (CAD) (1,2). However, the diagnostic yield of catheterization among stable patients with suspected CAD is low, even after previous noninvasive testing (3,4). The accuracy of functional testing declines as the prevalence of obstructive CAD in men and women...
referred for evaluation of their chest pain falls (5). Consequently, positive test results are more likely to be false positive results. Therefore, improved patient selection and diagnostic testing are both necessary to efficiently identify patients with obstructive disease who might benefit from such testing.

The coronary artery calcium (CAC) score is an inexpensive and low radiation (<1 mSv) test that is suitable to minimize unnecessary diagnostic testing (6). Absence of CAC in stable symptomatic individuals can identify subjects at low risk of cardiovascular disease and events. Among symptomatic patients, 20% to 50% were found to have a CAC score of zero (7,8). Further downstream testing in such patients has limited value (9,10). Although the frequency of ischemia increases with higher CAC scores, the CAC score itself does not differentiate obstructive disease from nonobstructive disease (11). Because guidelines recommend coronary revascularization only in patients with evidence of ischemia, additional tests are often warranted. To this end, cardiac stress tests are widely used for work-up of patients with suspected obstructive CAD and have the ability to induce myocardial ischemia during cardiac stress in the presence of hemodynamically significant CAD. Furthermore, they can guide coronary revascularization strategies.

Adenosine stress cardiac magnetic resonance (CMR) imaging is a popular noninvasive test for the detection of symptomatic obstructive CAD. It is attractive because of its lack of ionizing radiation and high spatial resolution (12,13). CMR accurately assesses myocardial perfusion. Stress myocardial perfusion imaging with CMR is more accurate in ruling out hemodynamically significant CAD than a single-photon emission computed tomography nuclear imaging test and exercise echocardiography (14). In low-risk patients, as in patients without previous myocardial infarction, normal CMR results have a high negative predictive value (1,2), and less comprehensive protocols may be sufficient to guide further work-up and therapy (15,16).

The aim of this study was to assess whether, in patients with stable chest pain, adenosine stress-only perfusion CMR, in addition to a positive CAC score, could serve as an effective gatekeeper before CAG testing and could improve the diagnostic yield of CAG. Our second aim was to investigate the association between positive CAC scores and stress-induced myocardial ischemia.

**METHODS**

**DESIGN OF THE STUDY.** Patients consecutively referred between December 2004 and May 2011 for evaluation of chest pain were included in this prospective consecutive registry. Men and women were eligible if they were older than 44 years of age and presented with stable symptoms. Patients with a history of myocardial infarction (MI), percutaneous coronary intervention, and coronary artery bypass grafting were excluded, as were patients with contraindications to adenosine perfusion CMR (17). All patients underwent computed tomography scanning for the determination of the CAC score. Patients with a CAC score of zero were excluded from the present analysis (18). Patients with a CAC score >0 underwent CMR. The final study population consisted of 642 patients (Figure 1). The Medical Review Committee confirmed the protocol was not subject to the Medical Research Involving Human Subjects Act and approved the protocol (METC 07076). The study design is extensively described in the Supplemental Appendix.

**ASSESSMENT OF RISK FACTORS.** The type of chest pain of the patients was classified on the predominant characteristics of their chest discomfort. Typical angina was defined in the presence of all of the following characteristics: substernal chest discomfort of characteristic quality and duration, as provoked by exertion or emotional stress and relieved by rest and/or nitrates within minutes. Atypical angina was diagnosed when 2 of these characteristics were met and nonanginal chest pain in cases of 1 or none (19).

Systemic arterial hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg, or treatment for hypertension. Dyslipidemia was defined as total cholesterol >6.0 mmol/l or treatment for dyslipidemia. Diabetes mellitus was diagnosed in the presence of hemoglobin A1c ≥48 mmol/mol, a fasting plasma glucose of ≥7.0 mmol/l, a random plasma glucose of >11 mmol/l, or the use of glucose-lowering medication. Smoking was self-reported. Family history of premature obstructive CAD was defined as a history of MI, percutaneous coronary intervention, or revascularization at younger than 60 years in a first-degree family member.

**CALCium SCORE.** A 16-row multiple detector computed tomography scanner (sensation 16, Siemens, Munich, Germany) was used to acquire a volume set of data of the heart according to a standard spiral protocol. Scans were made during maximal inspiration. CAC was measured by the Agatston method using dedicated software (20). We
classified CAC scores into 3 categories: 0.1 to 100 (low); 100 to 400 (medium), and $\geq 400$ (high).

**STRESS-ONLY, FIRST-PASS ADENOSINE CMR.** All scans were performed at 1.5-T using a Magnetom Avanto CMR system (Siemens Medical Solutions, Erlangen, Germany). The studies were done according to the institutional stress-only protocol at the time of the scan. All antianginal medication was stopped 4 days before the examination. Xanthine-containing products like coffee, tea, chocolate, and cola had to be stopped 24 h before the examination. Dipyridamole had to be stopped or was considered a contraindication. After 3 min of adenosine infusion (0.140 mg/kg/min) during the first pass of 0.1 mmol/kg gadopentetate dimeglumine with a flow rate of 5 ml/s flushed with 15 ml 0.9% sodium chloride (flow rate 5 ml/s), a perfusion sequence was started: TrueFisp: TR, 150.5/163.1 ms; TE 1.03 ms; TI 100/103 ms; $\alpha = 45/50^\circ$; field of view: 300 $\times$ 300; slice thickness 6 mm; matrix 76 $\times$ 128; and iPAT 2. Three short-axis slices were acquired (21). Because only patients without a history of MI were included in this study, late gadolinium enhancement (LGE) and rest perfusion were not routinely performed. Total duration of the protocol was approximately 15 min.

**IMAGE ANALYSIS.** Perfusion series were visually analyzed by an experienced radiologist and cardiologist in consensus, using a 16-segment model (22). A perfusion abnormality in at least 2 segments at consecutive planes of the left ventricle or 1 segment of the most apical slice was used as an indication for CAG. Patients with such a perfusion defect underwent CAG. The decision to proceed to percutaneous coronary intervention or coronary artery bypass grafting was made in consultation with the patient, cardiac surgeon, and interventional cardiologist.

**OUTCOME AND FOLLOW-UP.** The outcome of interest was the presence of obstructive CAD, defined as $\geq 50\%$ stenosis in at least 1 vessel on CAG. Otherwise, if CAG was not performed, the outcome of interest was the occurrence of early major adverse cardiovascular events (MACE) (23), which consisted of...
all-cause mortality, nonfatal MI, and coronary revascularization within 12 months after CMR.

Survival was assessed in May 2016 using the national Civil Registry. Surviving patients received a questionnaire to collect information on cardiac events and procedures. Potential clinical events were adjudicated after review of hospital records. The date of returning the questionnaire was used to calculate follow-up time. Three patients were lost to follow-up and were excluded from analysis.

DATA ANALYSIS. Baseline categorical variables are presented as absolute numbers and frequencies and continuous variables as mean ± SD. Sensitivity, specificity, and negative and positive predictive values were calculated. Odds ratios (ORs) for significant obstructive CAD were calculated by univariate and multivariate logistic regression analysis.

To investigate the added value of CAC scores and adenosine CMR to predict obstructive CAD, the following 3 models were used: model I (only clinical characteristics), model II (model I + CAC score), and model III (model II + adenosine CMR).

As a measure of discrimination, we calculated the area under the receiver-operating characteristics curve (C-index) with 95% confidence intervals (CIs) for diagnosis of significant obstructive CAD and early MACE. The added value of models II and III beyond the basic model was quantified by the change in the C-index.

RESULTS

PATIENTS. A total of 642 patients met the inclusion criteria and constituted our study population. Their mean age was 63 years, and 50% were women (Table 1). The number of smokers was 17%; 18% had diabetes mellitus. Typical angina was present in 19%, atypical angina in 32%, and nonanginal chest pain in 49%.

CAC SCORE, CAG, AND 1-YEAR OUTCOME. A CAC score between 0.1 and 100 was observed in 262 patients (41%); a CAC score between 100 and 400 was present in 214 (33%) patients, and a CAC score of ≥400 was seen in 166 (26%) patients.

The relationship of CAC score, type of chest pain, and obstructive CAD is shown in Table 2. A CAC score between 0.1 and 100 was associated with obstructive CAD in 6% of patients, compared with 13% of patients with a CAC score between 100 and 400 and 27% of patients with CAC score ≥400. In patients with typical angina and high CAC scores, 52% exhibited obstructive CAD, compared with 37% of patients with typical angina and an intermediate (between 100 and 400) CAC score and with 20% in such patients with a low (between 0.1 and 100) CAC score.

ADENOSINE STRESS-ONLY CMR, CAG, AND 1-YEAR OUTCOME. No major complications occurred during adenosine stress testing. A perfusion abnormality was present in 87 patients (14%). Additional rest perfusion was done in only 1% of patients. In patients presenting with nonanginal chest pain, 7% exhibited ischemia, whereas ischemia was present in 34% of patients with typical angina (Table 3). Most patients with ischemia underwent CAG. Obstructive CAD was found in 77 (92%) patients, whereas 7 (8%) patients exhibited no significant obstructions. Two patients with a fixed perfusion defect consistent with previous MI (n = 2) did not undergo CAG. In addition to the 79 patients with documented obstructive CAD, 8 other patients, with normal findings on adenosine CMR, had MACE within 1 year: 4 patients died (2 of cardiac causes); 1 patient experienced MI; and 3 patients underwent percutaneous coronary intervention. Thus, the total number of patients with either obstructive CAD or with early MACE amounted to 87 patients, encompassing 14% of the total population under study. For the diagnosis of confirmed obstructive CAD and MACE within 1 year, sensitivity of adenosine CMR was 90.9% (95% CI: 88.7% to 93.1%), with specificity of 98.7% (95% CI: 97.9% to 99.6%), a positive predictive value of 92% (95% CI:
TABLE 2  Significant CAD and Early MACE According to Type of Chest Pain and CAC Score

| Type of Chest Pain | Nonanginal | Atypical | Typical | Total |
|--------------------|------------|----------|---------|-------|
| No. of patients    | 315 (49.1)| 208 (32.4)| 119 (18.6)| 642 (100.0) |
| CAC score          |            |          |         |       |
| 0.1–1.00.0         | 138 (43.8)| 101 (32.1)| 76 (24.1)| 315 (49.1) |
| 1.00.0–4.00.0      | 79 (38.0)| 72 (34.6)| 45 (37.8)| 208 (32.4) |
| 4.00.0–10.0.0      | 15 (26.3)| 9 (20.0)| 15 (20.0)| 119 (18.6) |
| ≥10.0.0            | 4 (2.9)| 3 (3.0)| 9 (12.5)| 25 (3.9) |
| CAD or MACE*       | 1 (1.3)| 0 (0.0)| 0 (0.0)| 1 (0.2) |
| No CAD or MACE*    | 134 (97.1)| 98 (97.0)| 63 (82.9)| 262 (40.8) |

Values are n (%) or range. *Major adverse cardiovascular event(s) (MACE) within 1 year after a nonischemic CMR.

89.8% to 94.1%), a negative predictive value of 98.6% (95% CI: 97.6% to 99.5%), a positive likelihood ratio of 91, and negative likelihood ratio of 0.09.

PREDICTORS OF SIGNIFICANT CAD OR EARLY MACE. Among the clinical variables, sex, type of chest pain, and current smoking were associated with a combination of obstructive CAD and early MACE. A model that consisted of clinical variables only (model I) resulted in a C-index of 0.78 (95% CI: 0.72 to 0.83) (Figure 2). When the CAC score was added to the clinical variables (Table 4), the highest CAC score was independently and statistically significantly associated with obstructive CAD and early MACE compared with the lowest CAC score (OR: 7.52 95% CI: 3.54 to 15.98). Furthermore, the addition of the CAC score (model II) resulted in an increase in the C-index to 0.82 (95% CI: 0.77 to 0.87). The subsequent addition of CMR (model III) increased the level of the C-index to 0.97 (95% CI: 0.95 to 1.00).

DISCUSSION

The results of the present study demonstrated that stress-only adenosine CMR, in addition to a positive CAC score, in patients with stable chest pain and without a history of cardiac disease, can serve as an effective gatekeeper to identify ischemia and improve the diagnosis of obstructive CAD. CMR provided diagnostic value incremental to clinical data and CAC score, and CMR after CAC scoring accurately detected clinically significant obstructive CAD in patients with stable chest pain.

Furthermore, this study demonstrated the strong association of high CAC score with ischemia and early MACE. In the clinical work-up of patients with stable chest pain, the CAC score added relevant diagnostic value to clinical variables. As expected, with increasing CAC scores, corresponding increases on the severity of CAD were observed. In addition, a CAC score ≥400 was associated with an increased risk of significant obstructive stenosis, even in patients with nonanginal chest pain. Patients (52%) who presented with typical angina and a CAC score of ≥400 showed significant CAD.

Guidelines recommend noninvasive stress testing to determine the need for CAG in patients at low or intermediate risk of obstructive CAD. The pre-test likelihood can be helpful in the prediction of obstructive CAD but its use often leads to an overestimation of disease probability (24). As a result, there has been a marked decline in the frequency of inducible myocardial ischemia and obstructive CAD in patients referred for imaging tests over the last decade (25). Coronary computed tomography angiography allows for the noninvasive visualization of anatomic CAD and has a well-established negative predictive value. However, the specificity decreases with increasing amounts of coronary calcium. Furthermore, positive computed tomography angiograms may require additional tests, such as stress tests or the more invasive CAG, partly to identify false positives (26).

In this era of value-based health care, value can be achieved only if appropriate patients are selected for

TABLE 3  Adenosine CMR and Early MACE According to Type of Chest Pain

| Type of Chest Pain | Nonanginal | Atypical | Typical | Total |
|--------------------|------------|----------|---------|-------|
| No. of patients    | 315 (49.1)| 208 (32.4)| 119 (18.6)| 642 (100.0) |
| Adenosine CMR      |            |          |         |       |
| −                  | 294 (93.3)| 182 (87.5)| 79 (66.4)| 555 (86.4) |
| +                  | 21 (6.7)| 26 (12.5)| 40 (33.6)| 87 (13.6) |
| MACE/CAD           | 20 (6.3)| 27 (12.5)| 41 (35.3)| 88 (13.7) |

Values are n (%).

CMR = cardiac magnetic resonance; other abbreviations as in Table 2.
Symptomatic patients in our clinic, 45% had no detectable calcium (8). In the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) study, 51% of all symptomatic patients were found to have a CAC score of zero (7). Thus, CAC scanning significantly reduced the number of patients who required stress testing. Avoiding further downstream testing avoids exposing patients to unnecessary risk and provides significant financial savings (30). However, even after the exclusion of patients without coronary calcium, the prevalence of confirmed obstructive disease in our study was only 14%.

General practitioners usually refer patients with stable chest pain if the diagnosis is unclear or if antianginal drugs fail (31). Our results suggested that cost reduction and better patient value might be achieved if the CAC score was incorporated into the practice guideline “Stable angina pectoris” from the Dutch College of General Practitioners, because this would, without compromising safety, lead to less unnecessary referrals (31). Adamson et al. (32) showed that the use of a symptom-focused strategy, as endorsed by the National Institute for Health and Care Excellence guideline, resulted in a 3- to 4-fold increase in low-risk patients who could be deferred from further testing compared with a Bayesian risk type approach (33). In the National Institute for Health and Care Excellence guidelines, patients who present with nonanginal chest pain and a normal electrocardiogram are deferred from further testing. Our study indicated that patients with atypical symptoms and a low CAC score constituted a testing and if test results change management and lead to improvement of outcome or cost reduction (27). The CAC score could fulfill this role. The CAC score is a rapid low-cost and low-radiation test with no contraindications. Calcification of atherosclerotic plaque occurs from the fourth decade of life (28). In patients age 45 years or older, CAC is a highly sensitive marker for the presence of atherosclerosis and can function as a first gatekeeper to further testing. The CAC score reflects the result of all risk factors over a lifetime in individual patients. In contrast to CAD risk factors that predict future disease, the CAC score directly measures the current presence of atherosclerosis (6). A recent meta-analysis revealed that low CAC scores generally defined patients at low risk for manifesting inducible myocardial ischemia (11). Furthermore, the CAC score provides additional prognostic information. A CAC score of zero safely ruled out obstructive CAD in many stable symptomatic patients (8,9,29). These results were recently confirmed in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial (18). A substantial number of patients with stable chest pain had no detectable calcium and could be deferred from further testing. In a previous study of 385 stable symptomatic patients in our clinic, 45% had no

| TABLE 4 Logistic Regression Models of CAD and Early MACE |
|----------------|----------------|----------------|----------------|
|                | Univariate     | Model I        | Model II       |
|                | OR (95% CI)    | OR (95% CI)    | OR (95% CI)    |
| Age            | 1.01 (0.99–1.03) | 1.01 (0.98–1.03) | 0.98 (0.95–1.00) |
| Male           | 2.68 (1.64–4.36) | 2.53 (1.50–4.27) | 1.89 (1.09–3.28) |
| Type of chest pain |               |                |                |
| Nonanginal     | Ref.           | Ref.           | Ref.           |
| Atypical       | 2.11 (1.14–3.88) | 2.36 (1.26–4.41) | 2.33 (1.22–4.43) |
| Typical        | 8.05 (4.47–14.49) | 7.63 (4.15–14.02) | 9.64 (5.04–18.44) |
| Smoking        | 1.18 (1.02–1.36) | 1.18 (1.01–1.38) | 1.21 (1.03–1.42) |
| Dyslipidemia   | 1.18 (0.72–1.93) | 1.28 (0.74–2.21) | 1.12 (0.63–1.99) |
| Diabetes       | 0.88 (0.54–1.43) | 0.92 (0.52–1.62) | 1.04 (0.56–1.92) |
| Hypertension   | 1.47 (0.94–2.32) | 1.28 (0.77–2.11) | 1.14 (0.68–1.93) |
| Family history | 1.00 (0.99–1.02) | 1.00 (0.99–1.02) | 1.00 (0.98–1.03) |
| CAC score      | Ref.           | Ref.           |                |
| 0.1–100        | 1.00 (0.89–1.12) | 1.00 (0.89–1.12) | 1.00 (0.89–1.12) |
| 100–400        | 2.29 (1.21–4.36) | 2.72 (1.34–5.53) |                |
| ≥400           | 5.52 (3.00–10.18) | 7.52 (3.54–15.98) |                |
| C-index        | 0.78 (0.72–0.83) | 0.82 (0.77–0.87) |                |

*Model I: clinical variables; Model II: Model I + CAC score
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.
low-risk population as well. However, symptomatic patients with a CAC score >400 and nonanginal chest pain could benefit from further testing because 17% were diagnosed with significant obstructive CAD within 1 year.

The evidence for the usefulness of stress perfusion CMR is considerable (1,34). In a meta-analysis that compared cardiac imaging methods directly to fractional flow reserve, CMR had the highest performance for diagnosis of ischemia-causing obstructive CAD, whereas the anatomic methods of coronary computed tomography angiography and CAG yielded lower specificity (35). Meta-analysis showed that, when used in isolation, CMR had a sensitivity of 89% to 91% and a specificity of 76% to 87% (36–38). Stress-only adenosine CMR after the CAC score had a sensitivity of 90.9% and a specificity of 98.7%. The high negative predictive value of 98.6% allowed us to exclude patients with a negative stress-only adenosine CMR from further testing. The high sensitivity of CMR improved the diagnostic yield of CAG.

To the best of our knowledge, this was the first prospective study in which the CAC score was used as a gatekeeper before stress-only adenosine CMR. The strength of our study was that it represented the real world. All patients were included if they were symptomatic, had a CAC score >0, and were able to undergo CMR. In addition, we did not perform rest perfusion routinely because only patients without a history of obstructive CAD were included in this study. A resting perfusion scan is required in cases with uncertainty about the relevance of an abnormal stress perfusion result (39).

**STUDY LIMITATIONS.** The exclusion of patients with CAC score of zero was done in view of the favorable prognosis of such subjects, even in the presence of noncalcified plaque. Referral to CAG was clinically driven and occurred infrequently in the absence of CMR-detected ischemia. Thus, our protocol, with abnormal CMR findings driving CAG, might have caused lead bias. Measurement of fractional flow reserve during CAG was not performed routinely.
because evidence of ischemia was available (40). However, in patients with stable angina and risk factors for CAD, the use of adenosine CMR in guiding initial management of patient care has been shown to be noninferior to the use of invasive CAG combined with fractional flow reserve (41). We did not perform LGE routinely. A growing body of evidence points to the prognostic value of LGE. A study of mid-life risk factors with unrecognized and recognized MI detected 31 years later by LGE found unrecognized MI in 16.8% of such patients; therefore, routine LGE seems feasible for prognostic reasons (42). In another study, 10.7% of patients without a history of CAD showed scar on LGE (43). Therefore, we added early enhancement of myocardial scar with post-contrast T1 mapping to our protocol. However, no prognostic studies are available to compare the prognostic value of CAC score with LGE. Finally, this study was a single-center study, and the generalizability of the findings to other populations requires confirmation.

**CONCLUSIONS**

In this study of 642 consecutive patients with chest pain without previous MI, stress-only adenosine CMR was found to have high diagnostic accuracy. Such a protocol could reliably serve as an additional gatekeeper to CAG in patients with CAC scores of >0. Our study indicated that, in the absence of other clinical features that suggest high risk, patients with CAC scores between 0.1 and 100 and who have non-anginal or atypical angina could be deferred from further testing. Symptomatic patients with CAC scores of ≥400 showed significantly more ischemia in adenosine CMR, and functional testing should prove to be useful in these men and women, regardless of their type of chest pain (Central Illustration).

**REFERENCES**

1. Talix RA, Blomberg BA, El Aidi H, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. Circ Cardiovasc Imaging 2015;8:e002666.

2. Lipinski MJ, McVey CM, Berger JS, Kramer CM, Salerno M. Prognostic value of stress cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease: a systematic review and meta-analysis. J Am Coll Cardiol 2013;62:826–38.

3. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.

4. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.

5. Schmerrnund A, Bailey KR, Reumberger JA, Reed JE, Sheedy PF 2nd, Schwartz RS. An algorithm for noninvasive identification of angiographic three-vessel and/or left main coronary artery disease in symptomatic patients on the basis of cardiac risk and electron-beam computed tomographic calcium scores. J Am Coll Cardiol 1999;33:444–52.

6. Rozanski A, Berman DS. Coronary artery calcium scanning in symptomatic patients: Ready for use as a gatekeeper for further testing? J Nucl Cardiol 2017;24:835–8.

7. Villines TC, Hulten EA, Shaw LJ, et al. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero underlying coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. J Am Coll Cardiol 2011;58:2533–40.

8. Rijlaarsdam-Hermsen D, Kuipers D, van Dijkman PR. Diagnostic and prognostic value of absence of coronary artery calciumification in patients with stable chest symptoms. Netherlands Heart J 2011;19:222–8.

9. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. J Am Coll Cardiol Img 2009;2:675–88.

10. Engbers EM, Tinner JR, Ottervanger JP, Mouden M, Knollema S, Jager PL. Prognostic value of coronary artery calcium scoring in addition to single-photon emission computed tomographic myocardial perfusion imaging in symptomatic patients. Circ Cardiovasc Imaging 2016;9:e003966.

11. Bavishi C, Argulian E, Chatterjee S, Rozanski A. CACS and the frequency of stress-induced myocardial ischemia during MPI: a meta-analysis. J Am Coll Cardiol Img 2016;9:580–9.

12. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to

**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** In patients with chest pain the goal of testing is to initiate medical therapy, to consider coronary revascularization, and to identify patients at low risk for CAD. The absence of CAC almost rules out significant CAD in stable patients.

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS 1:** Careful clinical history taking and the CAC score may reduce the necessity of additional testing.

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS 2:** Stress-only adenosine CMR is an efficient and safe diagnostic imaging test with short scanning time.

**TRANSLATIONAL OUTLOOK 1:** Multicenter studies are necessary before incorporating the CAC score into clinical guidelines.

**TRANSLATIONAL OUTLOOK 2:** Cost-effectiveness after CAC score and stress-only adenosine CMR should be evaluated to ensure optimal safety and efficacy.

**ADDRESS FOR CORRESPONDENCE:** Dr. Jaap W. Deckers, Thoraxcenter, Division of Cardiology, Erasmus Medical Center, ‘s-Gravendijkwal 230, 3015 GD Rotterdam, the Netherlands. E-mail: j.deckers@erasmusmc.nl.
identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445-53.

13. Jerosch-Herold M, Muehling O, Wilke N. MRI of myocardial perfusion. Semin Ultrasound CT MRI 2006;27:2-10.

14. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC), a prospective trial. Lancet 2012;379:453-60.

15. Hachamovitch R, Rozanski A, Hayes SW, et al. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? J Nucl Cardiol 2006;13:768-78.

16. Uretsky S, Cohen R, Argulian E, et al. Combining stress-only myocardial perfusion imaging with coronary calcium scanning as a new paradigm for initial patient work-up: an exploratory analysis. J Nucl Cardiol 2015;22:89-97.

17. Hussain ST, Paul M, Plein S, et al. Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease. J Cardiovasc Magn Reson 2012;14:65.

18. Budoff MJ, Mayrhofer T, Ferencik M, et al. The prognostic value of coronary artery calcium in the PROMISE study. Circulation 2017;136:1993-2005.

19. Montalescot G, Sechtem U, Achenbach S, et al. The 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.

20. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.

21. Lubbers DD, Rijlaarsdam-Hermens D, Kuipers D, et al. Performance of adenosine “stress-only” perfusion MRI in patients without a history of myocardial infarction: a clinical outcome study. Int J Cardiovasc Imaging 2012;28:109-15.

22. Cerqueira MD, Weissman NJ, Dilisizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-42.

23. Labby A, Mace JC, Buncke M, MacArthur CJ. Quality of life improvement after pressure equalization tube placement in Down syndrome: a prospective study. Int J Pediatr Otorhinolaryngol 2016;88:168-72.

24. Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation 2011;124:2423-32.

25. Rozanski A, Gransar H, Hayes SW, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. J Am Coll Cardiol 2013;61:1054-65.

26. Meijis MF, Meiboom WB, Prokop M, et al. Is there a role for CT coronary angiography in patients with symptomatic angina? Effect of coronary calcium score on identification of stenosis. Int J Cardiovasc Imaging 2009;25:847-54.

27. Porter ME. What is value in health care? N Engl J Med 2010;363:2477-81.

28. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Arterioscler Thromb Vasc Biol 1995;15:1512-31.

29. Mouden M, Timmer JR, Reiffers S, et al. Coronary artery calcium scoring to exclude flow-limiting coronary artery disease in symptomatic stable patients at low or intermediate risk. Radiology 2013;269:77-83.

30. Lubbers M, Dedek A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. Eur Heart J 2016;37:1322-43.

31. Bouma B, Rutten FH, Boehn AM, Wiersma T. Summary of the practice guideline ‘Stable angina pectoris’ (second revision) from the Dutch College of General Practitioners [in Dutch]. Nederlands tijdschrift voor geneeskunde 2004;148:2221-5.

32. National Institute for Health and Care Excellence. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. National Institute for Health and Care Excellence, 2010. Available at: https://www.nice.org.uk/guidance/cg95. Accessed July 15, 2019.

33. Adamson PD, Newby DE, Hill CL, Coles A, Douglas PS, Fordyce CB. Comparison of international guidelines for assessment of suspected stable angina: insights from the PROMISE and SCOT-HEART. J Am Coll Cardiol Img 2018;11:1301-10.

34. Hendel RC, Friedrich MG, Schulz-Menger J, et al. CMR first-pass perfusion for suspected inducible myocardial ischemia. J Am Coll Cardiol Img 2016;9:1338-48.

35. Danad I, Szymonikta J, Twisk JW, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. Eur Heart J 2017;38:991-8.

36. Nandralur KR, Dwamena BA, Choudhri AF, Nandralur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. J Am Coll Cardiol 2007;50:1343-53.

37. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol 2012;59:1719-28.

38. Li M, Zhou T, Yang LF, Peng ZH, Ding J, Sun G. Diagnostic accuracy of myocardial magnetic resonance perfusion to diagnose ischemic stenosis with fractional flow reserve as reference; systematic review and meta-analysis. J Am Coll Cardiol 2014;7:1098-105.

39. Gibbons RJ, Balady GJ, Bentley JW, ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997;30:260-311.

40. Neumann FF, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:187-165.

41. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med 2019;380:2418-28.

42. McAravey D, Vidal JS, Aspelund T, et al. Midlife cardiovascular risk factors and late-life unrecognized and recognized myocardial infarction detect by cardiac magnetic resonance: ICEDLAND-MI, the AGES-Reyjavik Study. J Am Heart Assoc 2016;5:e004240.

43. van Dijk R, Kuipers D, Kaandorp TAM, et al. Accurate late gadolinium enhancement prediction by early T1-DT based quantitative synthetic mapping. Eur Radiol 2018;28:844-50.

KEY WORDS adenosine CMR, coronary artery calcium score, diagnosis, ischemia, stable chest pain

APPENDIX For an expanded Methods section, please see the online version of this paper.
Stress CMR and Combination Testing in the World of Multimodality Imaging*

Mark Westwood, MD,a Kristopher D. Knott, MBBSb

Coronary artery disease (CAD) remains a leading cause of mortality and morbidity, despite decades of improvement in diagnostic investigations and therapeutic interventions (1). Noninvasive imaging for the investigation of patients with chest pain is endorsed by the major U.S. and European Society guidelines and is often used to determine who gets referred for invasive coronary angiography (2,3). In stable patients, coronary artery calcium (CAC) score has been shown to have prognostic value. Patients with a CAC score of 0 have low event rates, and the cardiac event rate increases with an increasing CAC score (4,5). Cardiovascular magnetic resonance (CMR) using stress perfusion has been shown to be highly accurate for the detection of significant CAD, and a normal CMR result confers a good prognosis (6,7). However, with a lower pre-test probability, the likelihood of false positives increases.

In standard clinical practice, perfusion CMR includes vasodilator stress and rest perfusion (8). Reasons for rest perfusion include the ability to compare with stress perfusion in order to differentiate a true perfusion defect from the “dark rim” artifact (DRA) and to determine whether the perfusion defect is reversible (i.e., present at stress but not at rest) or fixed and matched (present at stress and rest), indicating an area of infarction. Additionally, the “splenic switch-off” sign, in which the spleen darkens with adequate stress and which suggests stress adequacy (9), can be seen. Whether these features are truly advantageous in the real world is debatable. The cause of DRA is multifactorial and likely down to a combination of Gibbs ringing artifact and cardiac motion (10,11). It is, thus, affected by heart rate and cardiac function, which often differ with the differing hemodynamic states at stress and rest. Also, there are other ways to differentiate DRA from a true perfusion defect, including the persistence of the defect and the intensity of it relative to that of pre-contrast images. With CMR, cine imaging and late gadolinium enhancement (LGE) are more reliable indicators of infarction, so the need to appreciate a reversible defect based on perfusion imaging is largely redundant. Finally, splenic switch-off can be seen on stress imaging alone and does not necessarily need a rest comparator. Stress-only CMR has previously been shown to be accurate in diagnosing CAD when read by experienced, level 3-accredited operators (12).

In this issue of iJACC, Rijlaarsdam-Hermsen et al. (13) enrolled 642 consecutive patients who did not previously have myocardial infarction or undergo percutaneous coronary intervention but were suspected of having CAD and a CAC score of 0 or stress-only CMR results. The CMR results determined whether they underwent invasive coronary angiography (13). Patients were followed for 1 year, and obstructive CAD was defined as ≥50% stenosis in a vessel by invasive coronary angiography or a major adverse cardiovascular event(s) (MACE) within 12 months of CMR (13). That study found obstructive CAD in 6% of patients with a CAC score of 0.1 to 100; 13% with a CAC score of 100 to 400; and 27% with a CAC score of ≥400 (13). A perfusion defect was detected in 87 patients (14%), and obstructive CAD was found in 77 of those patients (92%) (13). Eight patients with normal stress CMR results had a MACE during the follow-up period (13). That study found stress-only CMR results to be accurate with a sensitivity of 90.9%, a specificity of 98.7%, a positive

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the aBarts Heart Centre, St. Bartholomew’s Hospital, West Smithfield, London, United Kingdom; and the bInstitute of Cardiovascular Science, University College London, London, United Kingdom. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

ISSN 1936-878X/$36.00
had a perfusion defect on CMR and coronary v

There are limitations to the study, and they were acknowledged by the authors. First, only patients with a positive perfusion CMR underwent invasive angiography, a lead bias which potentially underestimates the number of false negatives. Additionally, the gold standard of angiographic stenosis of coronary vessels of $\geq 50\%$ has limitations, and no measurement of invasive physiology was made. Despite a highly selected cohort, only $14\%$ of patients had a perfusion defect on CMR findings. Also, LGE imaging was not performed, and that may be useful in detecting pathology and giving prognostic information in high-risk patients. Finally, a follow-up period $>1$ year would be desirable to increase confidence in the results.

Barriers to accessing CMR, particularly in developing countries, include the cost and availability of scans, and this is directly related to the time per scan. Other studies have shown the feasibility of 15-min CMR studies to improve accessibility and reduce cost (14). The authors of this current work can be commended for demonstrating that a 15-min stress-only scan is also feasible, which further breaks down barriers to access CMR (13).

Overall, the study adds to the growing evidence that stress-only CMR is sufficient in clinical practice. With advances in CMR including improved spatial resolution with k-t sequences (15) and absolute myocardial blood flow quantification with inline perfusion mapping (16,17), the advantages of including rest perfusion routinely are likely to further diminish in the future.

ADDRESS FOR CORRESPONDENCE: Dr. Mark Westwood, Barts Heart Centre, St. Bartholomew’s Hospital, London EC1A 7BE, United Kingdom. E-mail: markwestwood1@doctors.org.uk.

REFERENCES

1. World Health Organization. Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva: WHO; 2018.
2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44–164.
3. Knutti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes: the Task Force for the Diagnosis and Management of Chronic Coronary Syndromes of the European Society of Cardiology (ESC). Eur Heart J 2020;41:407–77.
4. Sanwar A, Shaw Li, Shapiro MD, et al. Diagnostiand prognostic value of absence of coronary artery calcification. J Am Coll Cardiol Img 2009;2:675–88.
5. Kelkar A, Schultz William M, Khosa F, et al. Long-term prognosis after coronary artery calcium scoring among low-intermediate risk women and men. Circ Cardiovasc Imaging 2016;9:e003742.
6. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol 2012;59:1719–28.
7. Greenwood JP, Herzog BA, Brown JM, et al. Prognostic value of cardiovascular magnetic resonance and single-photon emission computed tomography in suspected coronary heart disease: long-term follow-up of a prospective, diagnostic accuracy cohort study. Ann Intern Med 2016;160:1222.
8. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, for the Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on StandardizedProtocols. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson 2013;15:91.
9. Manisty C, Ripley DP, Herrey AS, et al. Splanchnic switch-off: a tool to assess stress adequacy in adenosine perfusion cardiac MR imaging. Radiology 2015;276:732–40.
10. Di Bella EVR, Parker DL, Sinunas AJ. On the dark rim artifact in dynamic contrast-enhanced MRI myocardial perfusion studies. Magn Reson Med 2005;54:1295–9.
11. Storey P, Chen Q, Li W, Edelman RR, Prasad PV. Band artifacts due to bulk motion. Magn Reson Med 2002;48:1028–36.
12. Villa ADM, Consinovski L, Ntalias I, et al. Importance of operator training and rest perfusion on the diagnostic accuracy of stress perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2018;20:74.
13. Rijlaarsdam-Hermsen D, Lo-Kioeng-Shioe M, van Domburg RT, Deckers JW, Kuipers D, van Dijkman PRM. Stress-only adenosine CMR improves diagnostic yield in stable symptomatic patients with coronary artery calcium. J Am Coll Cardiol Img 2020;13:1152–60.
14. Menacho K, Ramirez S, Segura P, et al. for the INCA (Peru) Study: Impact of non-invasive cardiac magnetic resonance assessment in the developing world. J Am Heart Assoc 2018;7:e008981.
15. Plein S, Ryf S, Schwitter J, Radjenovic A, Boesiger P, Kozierke S. Dynamic contrast-enhanced myocardial perfusion MRI accelerated with k-t sense. Magn Reson Med 2007;58:777–85.
16. Kellman P, Hansen MS, Nieles-Vallespin S, et al. Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. J Cardiovasc Magn Reson 2017;19:43.
17. Knott KD, Camaiioni C, Ramasamy A, et al. Quantitative myocardial perfusion in coronary artery disease: a perfusion mapping study. Magn Reson Imaging 2019;50:756–62.

KEY WORDS adenosine CMR, coronary artery calcium score, diagnosis, ischemia, stable chest pain
Identification and Quantification of Cardiovascular Structures From CCTA
An End-to-End, Rapid, Pixel-Wise, Deep-Learning Method

Lohendran Baskaran, MBBS,a,b,c,* Gabriel Maliakal, MSc,a,* Subhi J. Al’Aref, MD,a,b, Gurpreet Singh, PhD,a
Zhuoran Xu, MD, MSc,a; Kelly Michalak, BA,a; Kristina Dolan, BA,a; Umberto Gianni,a; Alexander van Rosendael, MD,a
Inge van den Hoogen,a Donghee Han,a; Wijnand Stuijfzand,a; Mohit Pandey, MSc,a; Benjamin C. Lee, PhD,a
Fay Lin, MD,a,b Gianluca Pontone, MD, PhD,a; Paul Knaapen, MD, PhD,a; Hugo Marques, MD, PhD,a
Jeroen Bax, MD, PhD,a; Daniel Berman, MD,d Hyuk-Jae Chang, MD, PhD,a; Leslee J. Shaw, PhD,a,b; James K. Min, MD,a,b

ABSTRACT

OBJECTIVES This study designed and evaluated an end-to-end deep learning solution for cardiac segmentation and quantification.

BACKGROUND Segmentation of cardiac structures from coronary computed tomography angiography (CCTA) images is laborious. We designed an end-to-end deep-learning solution.

METHODS Scans were obtained from multicenter registries of 166 patients who underwent clinically indicated CCTA. Left ventricular volume (LVV) and right ventricular volume (RVV), left atrial volume (LAV) and right atrial volume (RAV), and left ventricular myocardial mass (LVM) were manually annotated as ground truth. A U-Net–inspired, deep-learning model was trained, validated, and tested in a 70:20:10 split.

RESULTS Mean age was 61.1 ± 8.4 years, and 49% were women. A combined overall median Dice score of 0.9246 (interquartile range: 0.8870 to 0.9475) was achieved. The median Dice scores for LVV, RVV, LAV, RAV, and LVM were 0.938 (interquartile range: 0.887 to 0.958), 0.927 (interquartile range: 0.916 to 0.946), 0.934 (interquartile range: 0.899 to 0.950), 0.915 (interquartile range: 0.890 to 0.920), and 0.920 (interquartile range: 0.811 to 0.944), respectively. Model prediction correlated and agreed well with manual annotation for LVV (r = 0.98), RVV (r = 0.97), LAV (r = 0.78), RAV (r = 0.97), and LVM (r = 0.94) (p < 0.05 for all). Mean difference and limits of agreement for LVV, RVV, LAV, RAV, and LVM were 1.20 ml (95% CI: 7.12 to 9.51), 0.78 ml (95% CI: 10.08 to 8.52), 3.75 ml (95% CI: −21.53 to 14.03), 0.97 ml (95% CI: −6.14 to 8.09), and 6.41 g (95% CI: −8.71 to 21.52), respectively.

CONCLUSIONS A deep-learning model rapidly segmented and quantified cardiac structures. This was done with high accuracy on a pixel level, with good agreement with manual annotation, facilitating its expansion into areas of research and clinical import. (J Am Coll Cardiol Img 2020;13:1163–71) © 2020 by the American College of Cardiology Foundation.

From the "Dalio Institute of Cardiovascular Imaging, Weill Cornell Medicine, New York, New York;" Department of Radiology, New York–Presbyterian Hospital and Weill Cornell Medicine, New York, New York; "Department of Cardiovascular Medicine, National Heart Centre, Singapore;" Department of Imaging, Cedars-Sinai Medical Center, Cedars-Sinai Heart Institute, Los Angeles, California; "Department of Cardiology, Amsterdam AMC, Location VU University Medical Center, Amsterdam, the Netherlands;" Centro Cardiologico Monzino, IRCCS, Milan, Italy; "UNICA, Cardiac CT and MRI Unit, Hospital da Luz, Lisbon, Portugal;" Department of Cardiology, Heart Lung Center, Leiden University Medical Center, Leiden, the Netherlands; and the "Division of Cardiology, Severance Cardiovascular Hospital, Integrative Cardiovascular Imaging Center, Yonsei University College of Medicine, Seoul, South Korea. *Mr. Baskaran and Mr. Maliakal contributed equally to the content of this paper. The study was supported by the Dalio Institute of Cardiovascular Imaging. Dr. Lee has been a consultant for Cleerly. Dr. Bax has received speaker fees from Abbott Vascular and Boehringer Ingelheim. Dr. Min has received funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare; has served on the scientific advisory board of Arineta and GE Healthcare; and has an equity interest in Cleerly. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Joseph Schoepf, MD, served as Guest Editor for this paper.
The imaging of cardiac structures is essential in the diagnosis and progression of cardiovascular disease (CVD) and is a useful tool in monitoring progression and therapeutic response. Coronary computed tomography angiography (CCTA) provides rapid, noninvasive, isotropic whole-heart imaging with high-spatial resolution. Structural and functional parameters obtained from CCTA imaging correlate well with those from echocardiographic and cardiac magnetic resonance (CMR) (1,2). Although commercial software packages may provide semi-automated delineation of cardiac structures, substantial manual input is still required (3). This is time-consuming and may be operator-dependent.

Machine learning develops novel algorithmic strategies for the construction of inferential predictive models using large datasets, and its use in cardiac imaging is expanding (4). Within machine learning, deep learning is a subdomain that uses more sophisticated frameworks to perform automated feature (parameter) extraction. Using deep networks with many intermediate layers of artificial “neurons,” deep learning can model complex relationships between inputs and outputs. In this way, deep learning can substantially outperform systems that are dependent on experts or that are hand-crafted (5). In this study, we developed and evaluated an automated, end-to-end, deep-learning model for the identification and quantification of cardiovascular structures from CCTAs.

**METHODS**

**STUDY POPULATION.** The study population consisted of a randomly selected convenience sample aggregation of 2 international, multicenter, prospective observational registries that were described in detail elsewhere (6,7). Briefly, patients who underwent clinically indicated CCTA were included, with prospectively collected history, risk factors, and symptoms at baseline. Inclusion criteria were patients undergoing clinically indicated CCTA and age 18 years or older. Exclusion criteria were known coronary artery disease, hemodynamic instability, inability to provide consent, pregnancy, known adult congenital heart disease, baseline irregular heart rhythm, heart rate ≥100 beats/min, systolic blood pressure ≤90 mm Hg, contraindications to beta-blockers or nitroglycerin or adenosine, and uninterpretable CCTA. Each site obtained local institutional review board or ethics board approval.

**IMAGE ACQUISITION AND SEGMENTATION.** Scans were performed using ≥64 detector row scanners. Image acquisition, image post-processing, and data interpretation were performed according to current guidelines (8,9). Images were obtained and reconstructed at 0.50-mm intervals. Digital Imaging and Communications in Medicine files for site CCTAs were transmitted to a core laboratory, where annotation of the cardiac structures was done by level III experienced technologists who were blinded to all other data. Five cardiac structures were annotated in total using Adobe Photoshop (Adobe Systems, San Jose, California): left and right ventricular volume (LVV, RVV); left and right atrial volume (LAV, RAV); and left ventricular myocardial mass (LVM). LVV and RVV were delineated by the left and right ventricular endocardial borders, respectively. These excluded papillary muscles and trabeculations, and followed the contours below the atrioventricular plane valves on a 3-dimensional isotropic voxel level. LAV and RAV measurements included the appendage, but excluded adjacent veins, and were delineated by identifying the endocardial borders. LVM was calculated as the left ventricular myocardial volume derived by the delineation of its endocardial and epicardial borders and multiplied with the specific gravity of myocardial tissue (assuming a tissue density of 1.05 g/ml) (3). These annotations, which were established and verified by board-certified cardiologists, were used as the “ground truth” for the deep-learning model.

**SPLITTING OF DATASET AND PREPROCESSING.** The entire dataset containing 166 patients was split into 3 parts so that no 2 parts contained images from the same patient: training (70%, n = 132, 9,156 images); validation (20%, n = 34, 2,591 images); and testing (10%, n = 17, 1,477 images). The process of extraction of the ground truth from the annotated images was accomplished by an open source Python library known as “psd-tools” (10). The annotated slices were extracted from the annotated Photoshop files and were arranged according to the color coding.
assigned for each label. Because the Digital Imaging and Communications in Medicine volumes were converted to have an isotropic voxel spacing of $0.625 \times 0.625 \times 0.625$ mm, the extracted labels would also have the same isotropic resolution. As a preprocessing step, the images were windowed with a Hounsfield unit (HU) window ($-300$ to $500$) so that all structures to be segmented were sufficiently visible.

Each input image contained a pair of complementary label images. All the images and labels were then resized to $512 \times 512$ and passed to the model.

**DEEP-LEARNING MODEL.** The deep-learning architecture used was U-Net (11). This network was used for biomedical image segmentation in the past and demonstrated good performance on segmentation of organs in chest images (12). It consists of 4 layers in which the image is down sampled by a Conv$3 \times 3$ layer that consists of 2 runs through a set of component operations (convolution with $3 \times 3$ kernel, rectified linear unit, and a batch normalization layer) (Central Illustration). The resultant feature maps are down sampled by one-half the resolution by a $2 \times 2$ Max-pool layer. After 4 layers of this, the feature maps are up sampled by transposed convolution using a kernel size of $2$ and a stride of $2$, followed by successive Conv$3 \times 3$ blocks. The feature maps from the contracting path are concatenated with the up sampled feature maps of the expanding path. At the last layer, the feature maps are reduced from 128 to 2 using a Conv$1 \times 1$ block that consist of a $1 \times 1$ convolutional kernel; pixel-wise probabilities for belonging to each class is obtained once this is passed to a Softmax layer. Five separate but similar networks were trained for each structure (i.e., 1 network per structure).

**TRAINING STRATEGY AND MODEL EVALUATION.** The images were randomly shuffled and passed to the network with a batch size of 4 at a resolution of $512 \times 512$. The network was made to output binary masks for 2 classes (i.e., the foreground and the background). Dice loss was used to train the network. The Dice loss was calculated by subtracting the mean Dice similarity score from 1 (13). An Adam optimizer was used with a learning rate of 0.001 to carry out training (14). The outputs were compared with the ground truth that contained complimentary images of the contour of interest using the Dice loss. The network with the lowest Dice loss on the validation set was selected and evaluated on the test set. Each model was trained for 50 epochs. The model with the best validation loss was chosen among these epochs. The data were shuffled every epoch.

The image-based performance metric was based on Dice loss, calculated by subtracting the mean Dice similarity score from 1 (13). The Dice similarity score quantifies the pixel-wise degree of similarity between the model-predicted segmentation mask and the ground truth, and ranges from 0 (no similarity) to 1 (identical). Mathematically, it can be expressed as follows:
Dice similarity coefficient =
\[
\frac{(2 \cdot \text{True Positive})}{(2 \cdot \text{True Positive} + \text{False Positive} + \text{False Negative})}
\]

**STATISTICAL ANALYSIS.** Statistical analysis was performed using R version 3.5.0 (R Core Team, R Foundation, Vienna, Australia). Continuous and normally distributed variables were expressed by their mean ± SD and categorical data by their numbers (percentages). Levels of agreement between the model prediction and ground truth (manual annotation) were assessed on the test set with the Bland-Altman difference against mean plot. Pearson correlation’s test of volumes and mass between model prediction and ground truth were similarly assessed. Dice scores were summarized as medians and quartiles. Subgroup analysis of Dice scores by sex and age were compared by Wilcoxon’s test. A p value of <0.05 was considered significant.

**RESULTS**

The dataset consisted of 166 patients, with 13,224 images and 3,466 billion pixels. The cohort mean age was 61.1 ± 8.4 years, and 49% were women (Table 1). There were no significant differences for patient characteristics among the training, validation, and test sets (Supplemental Table 1). Mean LVV was 47.46 ± 20.27 ml, RVV was 65.44 ± 18.78 ml, LAV was 43.35 ± 13.25 ml, and RAV was 44.74 ± 14.37 ml (Table 2). Mean LVM was 69.95 ± 21.35 g. There were no significant differences between sexes or between ages younger than 65 years and 65 years or older for all parameters.

For all 5 structures (LVV, RVV, LAV, RAV, LVM), a combined overall median Dice score of 0.9246 (interquartile range: 0.8870 to 0.9475) was achieved on the validation set. Comparisons among the original image, manual annotation, and model prediction are shown in Figure 1. The median Dice scores for LVV, RVV, LAV, RAV, and LVM were 0.938 (interquartile range: 0.887 to 0.958), 0.927 (interquartile range: 0.916 to 0.946), 0.934 (interquartile range: 0.899 to 0.950), 0.915 (interquartile range: 0.890 to 0.920), and 0.920 (interquartile range: 0.811 to 0.944), respectively (Table 3). For LVV, although there was no significant difference in model prediction performance between the scores for male (0.923) and female (0.953) patients (p = 0.200), there was a difference between scores for ages younger than 65 years (0.958) and 65 years or older (0.834) (p = 0.002). For RVV, there were no significant differences between sexes (men = 0.916; women = 0.927) or age groups (age younger than 65 years = 0.927, age 65 years or older = 0.926). For the LAV, there were no significant differences in Dice scores between sex- or age-based subgroups (men = 0.918, women = 0.943; age younger than 65 years = 0.945, age 65 years or older = 0.918), nor were there differences for the RAV (men = 0.892, women = 0.917; age younger than 65 years = 0.915, age 65 years or older = 0.900) or the LVM (men = 0.855, women = 0.938; age younger than 65 years = 0.925, age 65 years or older = 0.850) (p > 0.05 for all). Automated segmentation for all 5 structures

| TABLE 1 | Baseline Characteristics (N = 166) |
|---|---|
| Age, yrs | 61.14 ± 8.38 |
| Female | 48.795 |
| Diabetes mellitus | 32.53 |
| Hypertension | 45.18 |
| Male | 46.65 ± 15.53 |
| Female | 48.36 ± 24.51 |
| Age < 65 yrs | 0.815 |
| Age ≥65 yrs | 0.200 |
| LVV (ml) | Overall |
| Female | 67.16 ± 22.20 |
| Age < 65 yrs | 0.749 |
| Age ≥65 yrs | 0.481 |
| RVV (ml) | Overall |
| Male | 63.91 ± 14.94 |
| Female | 67.16 ± 22.20 |
| Age < 65 yrs | 0.963 |
| Age ≥65 yrs | 0.277 |
| LAV (ml) | Overall |
| Male | 40.60 ± 12.92 |
| Female | 46.44 ± 12.93 |
| Age < 65 yrs | 0.423 |
| Age ≥65 yrs | 0.277 |
| LVM (g) | Overall |
| Male | 47.74 ± 16.57 |
| Female | 48.08 ± 16.43 |
| Age < 65 yrs | 0.541 |
| Age ≥65 yrs | 0.096 |

Table values are mean ± SD or %.

| TABLE 2 | Ground Truth Measurements |
|---|---|
| Structure/Category | p Value |
| LVV (ml) | Overall | 47.46 ± 20.27 |
| Male | 46.65 ± 15.53 |
| Female | 48.36 ± 24.51 |
| Age < 65 yrs | 0.815 |
| Age ≥65 yrs | 0.200 |
| RVV (ml) | Overall | 65.44 ± 18.78 |
| Male | 63.91 ± 14.94 |
| Female | 67.16 ± 22.20 |
| Age < 65 yrs | 0.749 |
| Age ≥65 yrs | 0.481 |
| LAV (ml) | Overall | 43.35 ± 13.25 |
| Male | 40.60 ± 12.92 |
| Female | 46.44 ± 12.93 |
| Age < 65 yrs | 0.423 |
| Age ≥65 yrs | 0.277 |
| LVM (g) | Overall | 44.74 ± 14.37 |
| Male | 41.78 ± 11.47 |
| Female | 48.08 ± 16.43 |
| Age < 65 yrs | 0.541 |
| Age ≥65 yrs | 0.277 |

Values are mean ± SD.

LVV = left ventricular volume; LVM = left ventricular myocardial mass; LAV = left atrial volume; RAV = right atrial volume; RVV = right ventricular volume.
took 13.13 s/patient, at 0.124 s/slice, whereas manual segmentation took approximately 1 h/patient. Intra-reader agreement was high with correlation coefficients for the LVV, RVV, LAV, RAV, and LVM of 0.999, 0.999, 0.998, 0.985, and 0.993, respectively. Correlation coefficients for inter-reader agreement for LVV, RVV, LAV, RAV, and LVM were 0.999, 0.995, 0.980, 0.978, and 0.993, respectively.

Overall, the model prediction for all structures correlated well with no significant differences compared with manual annotation ground truth. LVV as predicted by the model correlated well ($r = 0.98; p < 0.05$), with a difference in measurement of 1.19 ± 4.12 ml or 5.0 ± 13.0% ($p = 0.35$), as did RVV prediction ($r = 0.97; p < 0.05$), with a volume difference of 0.78 ± 4.60 ml or 1.3 ± 9.0% ($p = 0.85$). LAV correlated marginally less well ($r = 0.78; p < 0.05$), but there was still no significant difference between the model prediction and manual annotation (3.75 ± 8.80 ml or 8.0 ± 17.0%; $p = 0.28$). RAV correlated
On a pixel level, this model was able to identify cardiac structures with high accuracy, as reflected by high Dice scores. Although a previous study using CCTA had a Dice score of 0.92, it used a thresholding, rather than a deep-learning method, to segment the LAA (15). A deep-learning method to segment the same structure obtained a superior Dice score of 0.95, as did one that segmented the LVM, with a score of 0.91 (16,17). However, in contradistinction to these studies, the present study identified multiple structures. Although another study used deep learning for multiple structures with comparable accuracies to the present model, accuracy was evaluated on a lower resolution patch-level basis, with a single patch equivalent to 961 pixels (18). This might result in a large difference when measuring volumes of structures. The present model’s pixel-based accuracy translated with high correlation and narrow limits of agreement for practically meaningful measurements of cardiac structures. Although different in approach, a 3-dimensional, mesh-based segmentation model of the same structures performed more rapid segmentation in 4 s (19). A similar study segmented 2 additional structures in 20 patients and obtained a Dice score of 0.90 (20).

To have practical import, this model was evaluated with regard to volume and mass quantification of cardiac structures, with high correlation coefficients and low measurement differences. These margins err comparable or markedly narrower than those found in other deep-learning studies. Compared with the present study, a previous study using deep learning to quantify LVV and LVM in CMR showed larger differences, with wider limits of agreement (21). Another deep-learning CMR study of 20 patients showed comparable or lower agreement of LVV and LAV (22). A larger deep-learning CMR study tested on 196 patients found higher correlation than the present study ($r = 0.99$), but with significant underestimation of LVM and LVM, and with wider limits of agreement in the study by Tao et al. (23). In echocardiography, a larger study on LVV obtained a comparable correlation of 0.95 and absolute mean error of 9.5 ml (24). A nuclear myocardial perfusion feasibility study on 56 patients also obtained a comparable correlation of 0.91 (Dice score: 0.93) when segmenting the LVM (25).

In previous non-deep-learning studies, correlation coefficients were lower, not only between modalities, but between differing measurement methods within the same modality (26). Furthermore, the agreement between the present prediction model and the ground truth was comparable to inter- and intra-reader agreements in multiple other manual studies (3,27). A deep-learning model reproduced the same result

### TABLE 3 Model Performance

| Structure/Category | p Value |
|--------------------|---------|
| **LVV**            |         |
| Overall            | 0.938 (0.887-0.958) | — |
| Male               | 0.923 (0.742-0.942) | 0.200 |
| Female             | 0.953 (0.922-0.960) | — |
| Age <65 yrs        | 0.958 (0.942-0.965) | 0.002 |
| Age ≥65 yrs        | 0.834 (0.712-0.926) | — |
| **RVV**            |         |
| Overall            | 0.927 (0.916-0.946) | — |
| Male               | 0.916 (0.741-0.934) | 0.236 |
| Female             | 0.927 (0.925-0.956) | — |
| Age <65 yrs        | 0.927 (0.916-0.946) | 0.541 |
| Age ≥65 yrs        | 0.926 (0.683-0.940) | — |
| **LAV**            |         |
| Overall            | 0.934 (0.899-0.950) | — |
| Male               | 0.918 (0.493-0.945) | 0.167 |
| Female             | 0.941 (0.93-0.952) | — |
| Age <65 yrs        | 0.945 (0.928-0.950) | 0.167 |
| Age ≥65 yrs        | 0.918 (0.467-0.940) | — |
| **RAV**            |         |
| Overall            | 0.915 (0.890-0.920) | — |
| Male               | 0.892 (0.687-0.920) | 0.114 |
| Female             | 0.917 (0.914-0.943) | — |
| Age <65 yrs        | 0.915 (0.914-0.920) | 0.423 |
| Age ≥65 yrs        | 0.900 (0.661-0.938) | — |
| **LVM**            |         |
| Overall            | 0.920 (0.811-0.944) | — |
| Male               | 0.855 (0.580-0.935) | 0.093 |
| Female             | 0.938 (0.915-0.947) | — |
| Age <65 yrs        | 0.935 (0.90-0.945) | 0.139 |
| Age ≥65 yrs        | 0.850 (0.558-0.935) | — |

Values are median (25th to 75th quartiles).

Abbreviations as in Table 2.
every time, giving a hypothetical intra-reader agreement of 1.0.

This could benefit clinical workflow because it raises the future possibility of a deep-learning “second reader.” Double reading reduces variability and interpretative error, and results in clinically impactful decision changes, but is still sparsely implemented due to time and cost issues. The ability to segment structures may also allow computer-aided detection to evaluate abnormal cardiac structure morphology.

**FIGURE 2 Model Agreement and Correlation With Manual Annotation**

(A) Bland-Altman and (B) linear regression plots for the differences and agreement between the deep learning–predicted segmented quantities and the original ground truth manually annotated quantities. Abbreviations as in Figure 1.

**FIGURE 3 Incorrect Model Prediction**

An example of incorrect LAV prediction by the model (left to right): the original image, ground truth manual annotation (green), deep-learning model mask (red), and prediction overlaid on the image (red). Abbreviation as in Figure 1.
In addition, the rapid 13s throughput could allow future integration into clinical workflows with minimal disruption, helping to reduce workload burden for the imaging clinician and minimizing fatigue (28).

As such, this model tentatively portends clinical integration that increases interpretive speed at potentially low cost, while reducing sources of interpretive error.

**STUDY LIMITATIONS.** A limitation of this study was the cohort size. Although the study design included a hold-out 10% test set that was never seen until the final evaluation, this test set only included 17 patients. This hold-out set consisted of 1,477 images, which was more than amply acceptable for medical image-based, deep-learning applications (29). The high Dice score attested to the model’s robustness between these 2 groups, but overfitting could not be ruled out. Nevertheless, the model did make incorrect predictions (Figure 3). Furthermore, LVV wall prediction was significantly better in the younger than 65 years age group. Because the training, validation, and test sets were not significantly different, the difference in Dice score might perhaps be attributable to a higher prevalence of comorbidities that might have affected image quality (e.g., atrial fibrillation, respiratory disorders). This was outside the scope of the present study. A larger training and testing cohort and external validation will address these issues and improve real-world model performance. Integration of additional structures into the model (e.g., valves) will increase the applicability of the model. In addition, the scan timing of these images did not optimize contrast opacification of the RVV and RAV. Last, for image extraction and ease of integration into model architecture, annotation was done using Photoshop, instead of clinically conventional image annotation software, a gap that needs to be bridged for clinical integration.

**CONCLUSIONS**

An end-to-end, deep-learning model was able to detect and segment cardiac structures from CTA images with high accuracy when evaluated on a pixel level, as well as compared with manual measurement values. This was done in a rapid manner, potentiating expansion into areas of research and clinical import.

**ADDRESS FOR CORRESPONDENCE:** Dr. Lohendran Baskaran, Weill Cornell Medical College and the Dalio Institute of Cardiovascular Imaging, 413 East 69th Street, Suite 108, New York, New York 10021. E-mail: lob2008@med.cornell.edu.

**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** We developed and evaluated a rapid deep-learning method to segment and measure the 4 cardiac chambers and the left ventricular myocardium with good correlation and agreement to manual methods.

**TRANSLATIONAL OUTLOOK:** Manual measurement of cardiac structures is laborious. Deep learning allows rapid and robust performance of this task, allowing quicker and larger datasets and measurements to be gathered for research and clinical use.

**REFERENCES**

1. Lee SC, Ko SM, Song MG, Shin JK, Chee HK, Hwang HK. Morphological assessment of the aortic valve using coronary computed tomography angiography, cardiovascular magnetic resonance, and transthoracic echocardiography: comparison with intraoperative findings. Int J Cardiovasc Imaging 2012;28 Suppl 1: 33-44.
2. Greusen J, Zimmermann E, Grohmann A, et al. Head-to-head comparison of left ventricular function assessment with 64-row computed tomography, biplane left cineventriculography, and both 2- and 3-dimensional transthoracic echocardiography: comparison with magnetic resonance imaging as the reference standard. J Am Coll Cardiol 2012;59:1897-907.
3. Fuchs A, Mejdahl MR, Kühl JT, et al. Normal values of left ventricular mass and cardiac chamber volumes assessed by 320-detector computed tomography angiography in the Copenhagen General Population Study: Eur Heart J Cardiovasc Imaging 2016;17:1009-17.
4. Al’Aref SI, Anchouche K, Singh G, et al. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. Eur Heart J 2019;40:1975-86.
5. Hinton G. Deep learning—a technology with the potential to transform health care. JAMA 2018;320:1101-2.
6. Rivzi A, Hartaigh BØ, Knaapen P, et al. Rationale and design of the CREDENCE trial: computed Tomogphic evaluation of atherosclerotic Determinants of myocardial IsChEmia. BMC Cardiovasc Disord 2016;16:190.
7. Lee S-E, Chang H-J, Rivzi A, et al. Rationale and design of the Progression of Atherosclerotic Plaque Determined by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: a comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. Am Heart J 2016;182:72-9.
8. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8:342-58.
9. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr 2016;10:435-49.
10. Python package for reading Adobe Photoshop PSD files. Available at: psd-tools/psd-tools. Accessed March 10, 2019.
11. Ronneberger O, Fischer P, Brox T. U-Net: convolutional networks for biomedical image segmentation. In: Navab N, Hornegger J, Wells WM, Frangi AF, editors. Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015. New York: Springer International Publishing, 2015; p 234–41.

12. Javaid U, Dasnoy D, Lee JA. Multi-organ segmentation of chest CT images in radiation oncology: comparison of standard and dilated UNet. In: Blanc-Talon J, Helbert D, Philips W, Popescu D, Scheunders P, editors. Advanced Concepts for Intelligent Vision Systems. New York: Springer International Publishing, 2018; p 188–99.

13. Sudre CH, Li W, Vercauteren T, Ourselin S, Cardoso MJ. Generalised Dice overlap as a deep learning loss function for highly unbalanced segmentations. Available at: https://arxiv.org/abs/1707.03237. Accessed April 2, 2019.

14. Kingma DP, Ba J. Adam: a method for stochastic optimization. Available at: https://arxiv.org/abs/1412.6980. Accessed April 5, 2019.

15. Leventi C, Babin D, Velicki L, et al. Left atrial appendage segmentation from 3D CCTA images for occluder placement procedure. Comp Biol Med 2019;104:163–74.

16. Jin C, Feng J, Wang L, et al. Left atrial appendage segmentation using fully convolutional neural networks and modified three-dimensional conditional random fields. IEEE J Biomed Health Inform 2018;22:1906–16.

17. Zreik M, Lessmann N, van Hamersvelt RW, et al. Deep learning analysis of the myocardium in coronary CT angiography for identification of patients with functionally significant coronary artery stenosis. Med Image Anal 2018;44:72–85.

18. Dormer JD, Ma L, Halicek M, Reilly CM, Schreibmann E, Fei B. Heart chamber segmentation from CT using convolutional neural networks. Proc SPIE Int Soc Opt Eng 2018;10578.

19. Zheng Y, Barbu A, Georgescu B, Scheuering M, Comaniciu D. Four-chamber heart modeling and automatic segmentation for 3-D cardiac CT volumes using marginal space learning and steerable features. IEEE Trans Med Imaging 2008;27:1668–81.

20. Mortazi A, Burt J, Bagci U. Multi-planar deep segmentation networks for cardiac substructures from MRI and CT. Available at: https://arxiv.org/abs/1708.00983. Accessed March 10, 2019.

21. Curiale AH, Colaveccia FD, Mato G. Automatic quantification of the LV function and mass: a deep learning approach for cardiovascular MRI. Comp Methods Progr Biomed 2019;169:37–50.

22. Narang A, Mor-Avi V, Prado A, et al. Machine learning based automated dynamic quantification of left heart chamber volumes. Eur Heart J Cardiovasc Imaging 2019;20:541–9.

23. Tao Q, Yan W, Wang Y, et al. Deep learning-based method for fully automatic quantification of left ventricle function from cine MR images: a multivendor, multicenter study. Radiology 2018;290:81–8.

24. Leclerc S, Smitad E, Pedrosa J, et al. Deep learning for segmentation using an open large-scale dataset in 2D echocardiography. IEEE Trans Med Imaging 2019;38:2198–210.

25. Wang T, Lei Y, Tang H, et al. A learning-based automatic segmentation and quantification method on left ventricle in gated myocardial perfusion SPECT imaging: a feasibility study. J Nucl Cardiol 2019 Jan 28 [E-pub ahead of print].

26. Rheinheimer S, Reh C, Figiel J, Mahnken AH. Assessment of right atrium volume by conventional CT or MR techniques: which modality resembles in vivo reality? Eur J Radiol 2016;85:1040–4.

27. Maffei E, Messali G, Martini C, et al. Left and right ventricle assessment with cardiac CT: validation study vs. Cardiac MR. Eur Radiol 2012;22:1041–9.

28. Waite S, Scott J, Gale B, Fuchs T, Kolla S, Reede D. Interpretive error in radiology. Am J Roentgenol 2016;206:739–49.

29. Cho J, Lee K, Shin E, Choy G, Do S. How much data is needed to train a medical image deep learning system to achieve necessary high accuracy? Available at: https://arxiv.org/abs/1511.06348. Accessed April 6, 2019.

KEY WORDS coronary computed tomography angiography, deep learning, quantification

APPENDIX For a supplemental table, please see the online version of this paper.
Artificial Intelligence
From Scientific Curiosity to Clinical Precocity?*

Marly van Assen, MSc, PtD,a Ludo J. Cornelissen, MSc, PtDb

Currently, artificial intelligence (AI) is experiencing its second peak on the hype cycle, enabled by technological developments such as advances in computing power, algorithm design, and data storage capabilities. Deep learning-based algorithms show an impressive capacity for pattern recognition that has not gone unnoticed in medical research. In recent years, medical journals have seen a massive influx of papers using AI approaches to solve imaging tasks (1,2). However, although AI research and technology are progressing at a dazzling pace, clinical implementations of algorithmic decision-making systems are few and far between. In this Editorial Comment, we share our view on how AI systems might gain clinical acceptance and how the study by Baskaran et al. (3) in this issue of iJACC, is a good step forward in forging a bridge between the technical and clinical side of AI in the medical imaging field.

The field of radiology has always been driven by technological innovations and has shown great adaptive skills, which are again put to the test with the rise of AI. Cardiac imaging has especially proven an interesting field for AI researchers, containing many complex imaging and analysis procedures. With the use of AI, many of these processes can be optimized and automated, reducing work load, time to diagnosis, treatment and, not unimportantly, costs.

Many AI applications are described for cardiac imaging, from calcium scoring to prognostication. The literature has a tendency to shift its focus quickly to the most complex and intricate tasks, bypassing the importance of a good foundation. The study performed by Baskaran et al. (3) goes back to the foundation of almost all these applications, identification, and quantification of cardiovascular structures. The application described in this study is the backbone of more complicated applications and forms a solid basis for future research.

Most AI systems used in medical imaging are data-driven and based on supervised machine learning. Put simply, these systems consist of 2 main components: 1) the model itself (including many subtleties in the training process such as choice of loss function, number of training iterations, regularization/normalization strategies, and so on); and 2) the data used to train the model (including both raw imaging data and annotations). Both components are equally important, and both are only valuable in a complementary fashion. Clinicians and AI specialists can thus contribute to the development of an AI system in different ways, focusing on their respective strengths.

Unfortunately, communication between these 2 sides is far from fluent and, from time to time, they speak a completely different language. This is, for example, apparent in the different metrics used for assessing model performance, in which the technical specialists usually report segmentation performance by means of the Dice coefficient or a surface distance metric, a clinical audience is far more familiar with correlation coefficients and p values to measure performance. This study reports both, which enables both “sides” to not only absorb the results in the jargon they are most comfortable with, but hopefully also build toward a better understanding between both sides. Besides reporting the accuracy of the algorithm, this study also reports absolute values and mean differences between manually and AI-determined values. Whereas from a technical point...
of view, this holds little value, in clinical practice these differences can have a large effect on the clinical decision-making process. More important, in combination with the Dice score, it can give insight in when the minimal accuracy is reached for clinical implementation of an algorithm.

Mutual understanding and collaboration are imperative because the medical system is based on physicians’ ability to take well-informed decisions and convey their reasoning to colleagues and patients. With regulations trailing far behind the innovation process, physicians will still be held responsible for their decisions, even if they are based on AI algorithms in which they have little to no insight. It therefore remains extremely important to provide a functional understanding of the algorithms used in a clinical context.

The duality between clinicians and AI specialists is again shown in the dissemination of AI research. In general, there are 2 types of scientific publications (and publication platforms) when it comes to AI: technically oriented, focused on AI methodology and targeting an audience with in-depth algorithmic knowledge, and clinically oriented, focused on the clinical application and the implications for patient care, targeting clinicians with in-depth medical knowledge. The Baskaran et al. (3) article is an excellent example of where these 2 fields meet, providing clinical perspective while giving enough information about the algorithm, promoting reproducibility and allowing validation.

Interestingly, this does not mean that the study is on the forefront of either the model or data side. For instance, the model the authors use is a neural network with the U-Net architecture, which was developed in 2015 for image segmentation with biomedical imaging in mind. U-Nets have quickly become the method of choice for segmentation tasks in the medical domain. Owing to the high pace of developments in the field of deep learning in general, new and improved versions of U-Net have already been shown to increase model performance on various datasets (for instance the U-Net++ architecture) (4). Using a more recent architecture would probably have boosted the mean Dice coefficient by a couple of percentage points.

In addition, a key challenge in radiological data science is the 3-dimensional (3D) nature of the images. Model builders have several choices when it comes to handling the 3D volumes: 1) process it on a slice-by-slice basis (Baskaran et al. [3]); 2) use different models for the axial, sagittal, and coronal planes, which is known as the 2.5D approach (see for instance Mortazi et al. [5] for an application for cardiac structure segmentation); or 3) use a fully 3D network that takes volumetric input (e.g., 3D U-Net) (6). Accommodating this requires either chopping the data up into parts or reducing resolution, even on state-of-the-art GPUs. Methods 2 and 3 (partially) conserve 3D consistency, whereas method 1 does not. Generally speaking, methods 2 and 3 lead to higher performance (at least, when evaluated patient-wise and not slice-wise).

On the data side, there is a high demand for medical datasets with high-quality annotations (7,8). Part of the reason why deep learning took such a flight for natural image analysis is the existence of large datasets such as ImageNet (containing >1 million labeled images of everyday objects, divided over 1,000 different classes). Clinical implementation of all AI applications is based on 2 pillars, the actual accuracy and validity of these algorithms and the trust clinicians put in them. Although this article forms a good basis by including computed tomography angiography examinations from 2 different centers worldwide, only a limited number of patients were included, warranting further validation. Ground truth segmentation of all cardiac structures is time intensive and makes it difficult to create large databases in a reasonable timeframe; however, these are indispensable for the development of robust AI algorithms.

Several initiatives have been started to promote the optimization of AI applications, creating publicly available databases and algorithms. An interesting example is the Multi-Modality Whole Heart Segmentation challenge, held in 2017, featuring a publicly available dataset of computed tomography and magnetic resonance images with ground truth segmentations of cardiac structures. Segmentation algorithms were developed by teams from 10 different institutions and evaluated on the same test set, providing an excellent benchmark (see Zhuang et al. [9] for a summary of the results) and enabling reproducible AI research. The next step to ensure that the algorithm proposed by Baskaran et al. (3) ventures outside this research paper, hopefully into clinical practice, is to confirm its validity and reproducibility on benchmark datasets. In such an open-access setting, the clinical and technical side can combine their strengths to optimize and validate both dataset and algorithm, thus creating the optimal circumstances to promote the clinical adaptation of AI applications.

As the research field of AI matures, the times will come for clinicians and AI specialists to join forces and take AI applications from the catacombs of research to clinical day-to-day practice. To reach this
milestone, first, collaboration between clinicians and AI specialists is crucial. In addition, high-quality annotated datasets have to be collected, curated, and made available for algorithm development and benchmarking to researchers worldwide. Moving AI research to the public arena allows for the evaluation of the reproducibility and validity of AI algorithms, providing the clinicians responsible for clinical acceptance with ample data to ensure the added value and reliability of these algorithms.

ADDRESS FOR CORRESPONDENCE: Dr. Marly van Assen, Faculty of Medical Sciences, University of Groningen Medical Center, Hanzeplein 1, Groningen 9713GZ, the Netherlands. E-mail: marly.v.assen@gmail.com.

REFERENCES

1. Singh G, Al’Aref SJ, Van Assen M, et al. Machine learning in cardiac CT: basic concepts and contemporary data. J Cardiovasc Comput Tomogr 2018;12:192–201.
2. Litjens G, Ciompi F, Wolterink JM, et al. State-of-the-art deep learning in cardiovascular image analysis. J Am Coll Cardiol Img 2019;8:1549–65.
3. Baskaran L, Maliakal G, Al’Aref SJ, et al. Identification and Quantification of cardiovascular structures from CCTA: an end-to-end, rapid, pixel-wise, deep-learning method. J Am Coll Cardiol Img 2020;13:1163–71.
4. Zhou Z, Rahman Siddiquee MM, Tajbakhsh N, Liang J. UNet++: a nested U-net architecture for medical image segmentation. In: Stoyanov D, Taylor Z, Carneiro G, et al., editors. Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support. Cham: Springer International Publishing, 2018;3–11.
5. Mortazi A, Karim R, Rhode K, et al. Cardiac-NET: segmentation of left atrium and proximal pulmonary veins from MRI using multi-view CNN. In: Descoteaux M, Maier-Hein L, Franz A, et al., editors. Medical Image Computing and Computer-Assisted Intervention—MICCAI 2017. Cham: Springer International Publishing, 2017;377–85.
6. Çiçek Ö, Abdulkadir A, Lienkamp SS, et al. 3D U-net: learning dense volumetric segmentation from sparse annotation. In: Ourselin S, Joskowicz L, Sabuncu MR, et al., editors. Medical Image Computing and Computer-Assisted Intervention – MICCAI 2016. Springer International Publishing, Cham, 2016;424–32.
7. Thrall JH, Li X, Li Q, et al. Artificial intelligence and machine learning in radiology: opportunities, challenges, pitfalls, and criteria for success. J Am Coll Radiol 2018;15:504–8.
8. Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med 2019;380:1347–58.
9. Zhuang X, Li L, Payer C, et al. Evaluation of algorithms for multi-modality whole heart segmentation: an open-access grand challenge. Med Image Anal 2019;58:101537.

KEY WORDS artificial intelligence, cardiac imaging, CCTA
Interplay of Coronary Artery Calcium and Risk Factors for Predicting CVD/CHD Mortality

The CAC Consortium

Gowtham R. Grandhi, MD, MPH, a Mohammadhassan Mirbolouk, MD, b Zeina A. Dardari, MS, b Mouaz H. Al-Mallah, MD, MS c John A. Rumberger, MD, PhD d Leslee J. Shaw, PhD d Ron Blankstein, MD f Michael D. Miedema, MD, MPH e Daniel S. Berman, MD b Matthew J. Budoff, MD i Harlan M. Krumholz, MD, SM a j k Michael J. Blaha, MD, MPH b Khurram Nasir, MD, MPH, MS l

ABSTRACT

OBJECTIVES This study sought to evaluate the association and burden of coronary artery calcium (CAC) with long-term, cause-specific mortality across the spectrum of baseline risk.

BACKGROUND Although CAC is a known predictor of short-term, all-cause mortality, data on long-term and cause-specific mortality are inadequate.

METHODS The CAC Consortium cohort is a multicenter cohort of 66,636 participants without coronary heart disease (CHD) who underwent CAC testing. The following risk factors (RFs) were considered: 1) current cigarette smoking; 2) dyslipidemia; 3) diabetes mellitus; 4) hypertension; and 5) family history of CHD.

RESULTS During the 12.5-years median follow-up, 3,158 (4.7%) deaths occurred; 32% were cardiovascular disease (CVD) deaths. Participants with CAC scores $\geq 400$ had a significantly increased risk for CHD and CVD mortality (hazard ratio [HR]: 5.44; 95% confidence interval [CI]: 3.88 to 7.62; and HR: 4.15; 95% CI: 3.29 to 5.22, respectively) compared with CAC of 0. Participants with $\geq 3$ RFs had a smaller increased risk for CHD and CVD mortality (HR: 2.09; 95% CI: 1.52 to 2.85; and HR: 1.84; 95% CI: 1.46 to 2.31, respectively) compared with those without RFs. Across RF strata, CAC added prognostic information. For example, participants without RFs but with CAC $\geq 400$ had significantly higher all-cause, non-CVD, CVD, and CHD mortality rates compared with participants with $\geq 3$ RFs and CAC of 0.

CONCLUSIONS Across the spectrum of RF burden, a higher CAC score was strongly associated with long-term, all-cause mortality and a greater proportion of deaths due to CVD and CHD. Absence of CAC identified people with a low risk over 12 years of follow-up, with most deaths being non-CVD in nature, regardless of RF burden.

(J Am Coll Cardiol Img 2020;13:1175–86) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.
Appropriate risk assessment is a critical first step in risk assessment and subsequent management decisions for cardiovascular disease (CVD), which is the leading cause of death in the United States and worldwide (1). Most risk assessment algorithms, including the Pooled Cohort Equations atherosclerotic cardiovascular disease (ASCVD) risk algorithm, use a traditional risk factor (RF)-based approach to estimate 10-year ASCVD risk to guide preventive pharmacotherapy (2,3). Despite the value of traditional RFs and the usefulness of the Pooled Cohort Equations as a starting point for risk estimation, many high- and low-risk individuals are mischaracterized as low and high risk by the traditional RF-based algorithms, which leads to overuse or underuse of preventive strategies (4–7).

The 2018 American Heart Association/American College of Cardiology cholesterol guidelines provided a Class Iia recommendation for coronary artery calcium (CAC) testing for individuals who had a risk-based treatment decision is unclear (3). Studies demonstrated the CAC score significantly improved risk prediction above and beyond conventional RFs (7–11). Absence of CAC is associated with an extremely low event rate despite having a high RF burden, thereby re-classifying these individuals as low risk for ASCVD (11,12). This ability of absence of CAC has been described as “power of zero.” In addition, the presence and severity of CAC has been shown to strongly predict adverse outcomes, including all-cause mortality during 5 to 10 years of follow-up. However, whether CAC has differential association with subspecific mortality causes beyond 10 years of follow-up has not been studied.

Therefore, we aimed to examine the association of CAC with cause-specific mortality across baseline risk and to identify the prognostic value of high CAC among individuals without RFs and a CAC score of zero among high-risk individuals using data from the CAC Consortium.

METHODS

STUDY PARTICIPANTS. The CAC Consortium is a multicenter retrospective cohort study of 66,636 participants free of coronary heart disease (CHD) who were referred for CAC testing between 1991 and 2010 (13). Consent was obtained before CAC scanning, and institutional review board approval for coordinating center activities, including death ascertainment, was obtained at Johns Hopkins Hospital (Baltimore, Maryland). Participants were determined to be free of CHD based on their history and evaluation by the referring physician. Individual patient-level demographic and clinical data were collected using a semi-structured in-person interview during the CAC scan and/or from an established diagnosis recorded in the electronic medical record (13).

Comparison of the CAC Consortium with the National Health and Nutrition Examination Survey 2001 to 2002, the MESA (Multi-Ethnic Study of Atherosclerosis) trial, and the Framingham Offspring/Third Generation study have been previously published (13). The CAC Consortium had a higher proportion of men (67%) compared with these cohorts (44% to 48%) and a predominantly white population (89%). The prevalence of traditional RFs was otherwise similar to the MESA cohort, except for a mildly higher prevalence of hypertension (45% vs. 31%), diabetes (13% vs. 7%), and smoking (13% vs. 10%) compared with the CAC Consortium.

RFs DATA COLLECTION. The following RFs were considered: 1) hypertension, which was defined as a self-reported or existing medical record diagnosis of hypertension, or current treatment with antihypertensive medication; 2) dyslipidemia, which was defined as a previous diagnosis of primary hyperlipidemia or dyslipidemia (elevated triglycerides and/or low high-density lipoprotein cholesterol [HDL-C]), treatment with any lipid-lowering drug, or low-density lipoprotein cholesterol (LDL-C) >160 mg/dl, HDL-C <40 mg/dl in men and <50 mg/dl in women, or fasting triglycerides >150 mg/dl in those with concomitant lipid values; 3) current cigarette

been a member of the advisory board for Element Health; has been a member of the Physician Advisory Board for Aetna; has received contracts from the Centers for Medicare and Medicaid; has received research grants from Medtronic, Johnson & Johnson, and the Food and Drug Administration; has been a member of the advisory board for Facebook; has a research agreement with the Shenzhen Center for Health Information; and has research collaboration with the National Center for Cardiovascular Diseases, Beijing. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Harvey Hecht, MD, served as Guest Editor for this paper. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

Manuscript received March 14, 2019; revised manuscript received July 25, 2019, accepted August 23, 2019.
smoking, which was defined as smoking at the time of CAC assessment; 4) diabetes mellitus, which was defined as a self-reported or existing medical record diagnosis of diabetes or treatment with oral hypoglycemic drugs or insulin; and 5) a family history of CHD, which was predominantly determined by a first-degree relative with a history of CHD, whereas 11% of the study population used a definition of premature family history (younger than 55 years of age in male relatives and younger than 65 years of age in female relatives). Multiple imputation was conducted in cases of partially missing RF data using a previously published algorithm (13). At least 1 RF was missing in 28% of the cohort. All analyses were repeated in the subpopulation with non-missing RF information.

**Computed Tomography Data.** Noncontrast cardiac-gated computed tomography scans for CAC scoring were performed at each site according to a common standard protocol for each scanner technology. Approximately 93% of participants were scanned using electron beam computed tomography, whereas the remaining scans were performed using multidetector computed tomography. Studies demonstrated no clinically meaningful differences between CAC scores derived from electron beam computed tomography versus multidetector computed tomography scans (14). CAC was quantified using the Agatston method in all participants (15).

**Follow-Up and Death Ascertainment.** Median follow-up was 12.5 years (interquartile range: 10.6 to 14.1 years), with maximum follow-up across sites ranging from 13.6 to 22.5 years. Ascertainment of death was conducted by linkage to the Social Security Death Index Death Master File using an algorithm previously validated in the Henry Ford Exercise Testing project (16). Cause of death was obtained via coded death certificates obtained from the National Death Index. Cause of death was reported using International Classification of Disease-9 and -10 codes and grouped as previously described (13). Internal validation studies against known deaths identified via the electronic medical record revealed >90% specificity for identifying known deaths, with an estimated sensitivity of 72% to 90%. A detailed comparison of death rates in the CAC Consortium with the U.S. Census and MESA study was previously published (13). The death rate in the CAC Consortium dataset was mildly but systematically lower than the white population from the MESA study; however, differences were diminished from 26.7% to 11.7% when limited to those within income above the poverty level, which might be more representative of the CAC Consortium. The death rates in the CAC Consortium were lower than that in the general U.S. white population, similar to previous comparisons of research studies and clinical patients in the general unselected population (16).

**Statistical Methods.** The baseline characteristics of study participants are presented as mean ± SD for continuous variables (age) and proportionate frequencies for categorical variables, and were compared using analysis of variance and chi-square analysis, respectively, across CAC score groups (0, 1 to 100, 100 to 400, and >400). Graphical analysis was used to display crude mortality, as well as proportion of deaths due to CHD versus CVD versus non-CVD.

### Table 1: Baseline Characteristics of Study Population by CAC Score Group in CAC Consortium

| Total Population (N = 66,636) | CAC = 0 (n = 29,757) (45%) | CAC 1–100 (n = 20,534) (31%) | CAC 100–400 (n = 9,067) (13%) | CAC >400 (n = 7,278) (11%) |
|-------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Age, yrs                      | 54 ± 11                     | 50 ± 9.2                    | 55 ± 9.5                    | 60 ± 9.5                    | 64 ± 9.7                    |
| Male                          | 67                           | 56                          | 73                          | 78                          | 84                          |
| Hypertension                  | 31                           | 23                          | 32                          | 40                          | 50                          |
| Dyslipidemia                  | 54                           | 48                          | 57                          | 61                          | 66                          |
| Diabetes mellitus             | 7                            | 4                           | 7                           | 10                          | 15                          |
| Current smoking               | 10                           | 9                           | 10                          | 11                          | 11                          |
| Family history of CHD         | 46                           | 46                          | 46                          | 46                          | 47                          |
| CAC score                     | 164 ± 480                    | 0                           | 28 ± 27                     | 211 ± 84                    | 1,156 ± 976                 |
| Race                          |                             | (n = 42,964) (n = 19,087)   | (n = 13,221) (n = 5,935)    | (n = 4,721)                 |
| White                         | 89                           | 89                          | 89                          | 90                          | 89.5                        |
| Asian                         | 4                            | 4                           | 3.5                         | 3                           | 3.5                         |
| Black                         | 2                            | 2                           | 2.5                         | 2                           | 2                           |
| Hispanic                      | 3                            | 3                           | 3                           | 2.5                         | 3                           |
| Others                        | 2                            | 2                           | 2                           | 1.5                         | 2                           |

Values are mean ± SD or n.

CAC = coronary artery calcium; CHD = coronary heart disease.
The risk factor (RF) burden increased (p < 0.001). The participants were more likely to have higher coronary artery calcium (CAC) scores as the risk factor (RF) burden increased (p < 0.001).

Across RF and CAC score groups. Annualized mortality rates were estimated by dividing the number of deaths by the total number of person-years at risk. Cumulative hazard analysis was performed using individual subject time-to-all-cause and/or cause-specific mortality data. The Nelson-Aalen estimator was used to generate the cumulative probability of mortality curves stratified by categories of CAC scores and RFs. Multivariable Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to evaluate the effect of CAC or RF burden on all-cause mortality. Fine and Gray subdistribution HR models were used for cause-specific mortality, which accounted for competing causes of death (17). Harrell’s concordance statistic (C-statistic) was estimated as a summary measure of risk discrimination.

To evaluate the prognostic value of high CAC among low-risk participants (no RFs) and CAC of 0 among high-risk patients (≥3 RFs), annual mortality rates and adjusted HRs were compared, stratified by RF burden and CAC score group. In sensitivity analysis, all analyses were performed using only non-imputed RF data for comparison. A p value < 0.05 was considered statistically significant for all the analyses. All statistical analyses were performed using STATA version 14 (STATA Corp., College Station, Texas).

RESULTS

The mean age of the study population was 54 ± 11 years, and 67% were men. Overall, 17% of the participants did not have any RFs, 36% had 1 RF, 32% had 2 RFs, and 15% had ≥3 RFs. Approximately 45% of the participants had CAC of 0, 31% had CAC of 1 to 100, 13% had CAC of 100 to 400, and 11% had CAC ≥400. Table 1 describes the baseline characteristics of the study population by CAC score strata. With worsening CAC score, the proportion of men, and those with hypertension, diabetes, and dyslipidemia increased. Among participants with CAC of 0, 56% were men, 23% had hypertension, 4% had diabetes, and 48% had dyslipidemia compared with 84%, 50%, 15%, and 66%, respectively, among those with CAC ≥400.

Figure 1 describes the prevalence of CAC according to the burden of RFs. Among the participants without RFs, 56% had CAC of 0, whereas 28%, 10%, and 6% had CAC scores of 1 to 100, 100 to 400, and ≥400, respectively. In those with ≥3 RFs, 30%, 31%, 19%, and 20% had CAC of 0, 1 to 100, 100 to 400, and ≥400, respectively. The participants were more likely to have higher CAC scores as RF burden increased. Only 6% had CAC ≥400 among those without RFs, whereas 8%, 12%, and 20% had CAC ≥400 in those with 1 RF, 2 RFs, and ≥3 RFs, respectively.

Burdens of CAC on all-cause and cause-specific mortality across baseline risk. Overall, 3,158 (4.74%) deaths were recorded over a median follow-up of 12.5 years (interquartile range: 10.6 to 14.1 years). CVD resulted in 971 deaths (31%), and 524 (16%) of those were due to CHD. Table 2 depicts the annualized mortality rates and HRs, with increasing RF burden and CAC score groups. The annualized all-cause mortality rate was 1.61 (95% CI: 1.49 to 1.74) deaths per 1,000 person-years for those with CAC of 0 compared with 13.16 (95% CI: 12.40 to 13.96) deaths per 1,000 person-years among those with CAC ≥400 (8-fold increase).

Similarly, a 16- and 23-fold increase in annualized CVD and CHD mortality rates, respectively, was seen among participants with CAC scores of ≥400 compared with participants with CAC of 0. The annualized CVD mortality rate was 0.33 (95% CI: 0.27 to 0.39) death per 1,000 person-years among those with CAC of 0 compared with 5.22 (95% CI: 4.75 to 5.74) deaths per 1,000 person-years among those with CAC ≥400 (16-fold increase). The annualized CHD mortality rate was 0.14 (95% CI: 0.10 to 0.18) death per 1,000 person-years among those with CAC of 0 compared with 3.19 (95% CI: 2.83 to 3.60) deaths per 1,000 person-years among those with CAC ≥400 (23-fold increase).

The annualized all-cause mortality rate per 1,000 person-years was 2.8 (95% CI: 2.54 to 3.09) in
participants with 0 RFs compared with 3.20 (95% CI: 3.00 to 3.41), 3.97 (95% CI: 3.74 to 4.22), and 6.60 (95% CI: 6.11 to 7.04) deaths per 1,000 person-years among those with 1, 2, and ≥3 RFs, respectively. A 2-fold increase in the annualized all-cause mortality rate and 3- to 4-fold increase in CVD and/or CHD mortality rates was seen among participants with ≥3 RFs compared with those with 0 RFs (Table 2).

The HRs for all-cause mortality were increased 1.43-fold (CVD mortality) and 2.09-fold (CHD mortality) for those with ≥3 RFs compared with CAC of 0. Similarly, participants without RFs but with CAC ≥400 had a high all-cause mortality rate of 11.50 deaths per 1,000 person-years compared with 2.25 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. Participants without RFs but with CAC ≥400 also had a high CHD mortality rate of 2.45 deaths per 1,000 person-years compared with 0.56 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. Participants without RFs but with CAC ≥400 had a high CVD mortality rate of 4.65 deaths per 1,000 person-years compared with 0.56 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. Participants without RFs but with CAC ≥400 also had a high CHD mortality rate of 2.45 deaths per 1,000 person-years compared with 0.22 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. Similarly, participants without RFs but with CAC ≥400 had a high all-cause mortality rate of 11.50 deaths per 1,000 person-years compared with 2.25 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. On further analysis, stratified by sex, women had higher mortality rates compared with men, although they had similar trends in mortality rates across all-cause and cause-specific mortality (Supplemental Figure 1).

**PROGNOSTIC VALUE OF HIGH CAC AMONG LOW-RISK PARTICIPANTS AND CAC OF 0 AMONG HIGH-RISK PARTICIPANTS.** Figure 2 and Supplemental Table 1 show the annualized mortality rate with increasing CAC scores according to RF burden. Participants with CAC of 0 but without RFs had the lowest all-cause and cause-specific mortality rates, whereas participants with CAC ≥400 and ≥3 RFs had the highest all-cause and cause-specific mortality rates. Participants without RFs but with CAC ≥400 had a high CVD mortality rate of 4.65 deaths per 1,000 person-years compared with 0.56 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. Participants without RFs but with CAC ≥400 also had a high CHD mortality rate of 2.45 deaths per 1,000 person-years compared with 0.22 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. Similarly, participants without RFs but with CAC ≥400 had a high all-cause mortality rate of 11.50 deaths per 1,000 person-years compared with 2.25 deaths per 1,000 person-years among participants with ≥3 RFs and CAC of 0. On further analysis, stratified by sex, women had higher mortality rates compared with men, although they had similar trends in mortality rates across all-cause and cause-specific mortality (Supplemental Figure 1).
Figures 3A and 3B depicts the absolute proportion and proportion of all deaths attributable to specific causes (non-CVD, CHD, and non-CHD CVD). Across RF groups, the proportion of deaths due to CHD and/or CVD increased significantly with increasing CAC score. The proportion of CHD mortality was 7% to 10% among those with CAC of 0, whereas it was 21% to 29% in those with CAC ≥400 across the RF burden. In contrast, there was a smaller increase in CHD and/or CVD mortality with an increase in the RF burden within each CAC score group. As shown in the Central Illustration, among participants with CAC of 0, most deaths were non-CVD related, despite the RF burden: non-CVD mortality was 83% and 75% among those with 0 RFs and ≥3 RFs, respectively. However, among participants with CAC ≥400, approximately 60% of the deaths were non-CVD related, despite the RF burden (Central Illustration).

Supplemental Figures 2 to 5 show increased all-cause, non-CVD, CVD, and CHD cumulative hazard curves with increasing CAC scores at each level of baseline RF burden. Among those with CAC ≥400 had a 1.84- to 3.2-fold higher risk of all-cause mortality across increasing RF burden compared with those with CAC of 0 and 1.6- to 2.6-fold higher risk for non-CVD mortality. However, the HRs for CVD mortality were 3.2- to 5.1-fold higher and those for CHD mortality were 3.8- to 8.7-fold higher in CAC ≥400 compared with CAC of 0 across increasing RFs (Table 3). By comparison, on analyses adjusted for age and sex, only ≥3 RFs were associated with a higher HR of all-cause, CVD or CHD mortality compared with 0 RFs among participants with a CAC >0, whereas no such higher risk was observed among participants with CAC of 0 (Table 4).

In sensitivity analyses, adjustment for the study site did not change the results, and additional analyses showed identical conclusions when only the nonimputed dataset was used.

**DISCUSSION**

In this large multicenter cohort of 66,636 asymptomatic individuals, we demonstrated that CAC predicts all-cause, CVD, and CHD mortality better across the spectrum of traditional RFs over a median follow-up of 12.5 years and a significant heterogeneity in subclinical coronary atherosclerosis across increasing RFs. Across baseline risk, CAC score was strongly associated with all-cause, CVD, and CHD mortality rates. Moreover, absence of CAC projected extremely
FIGURE 3  Cause-Specific Mortality With Increasing CAC Score

(A) Cause-specific proportion mortality of participants with increasing CAC score according to the burden of RF in the CAC Consortium. Within each RF group, the absolute proportion of CVD and CHD mortality increased with worsening CAC score. (B) Proportion of cause-specific mortality with increasing CAC score according to the burden of RF in the CAC Consortium. Within each RF group, the proportion of CVD and/or CHD mortality increased with increasing CAC score. Abbreviations as in Figures 1 and 2.
CENTRAL ILLUSTRATION  Mortality Rate (per 1,000 Person-Years) of Participants With CAC

A

Total Study Population
n = 66,636

0 RF (17%)  
n = 11,428

1 RF (36%)  
n = 23,726

2 RF (32%)  
n = 21,276

≥3 RF (15%)  
n = 10,206

Prevalence of CAC = 0
56%

All-cause mortality rate
1.42

0.10
0.13
0.23
0.34

83%
82%
77%
75%

1.18
1.24
1.27
1.69

0.15
0.15
0.23
0.34

10%
10%
14%
16%

7%
8%
9%
9%

10%
10%
14%
14%

1.88
1.87
1.87
1.87

6.67
6.67
6.67
6.67

Non-CVD Mortality  Non-CHD, CVD Mortality  CHD Mortality

B

Total Study Population
n = 66,636

0 RF (17%)  
n = 11,428

1 RF (36%)  
n = 23,726

2 RF (32%)  
n = 21,276

≥3 RF (15%)  
n = 10,206

Prevalence of CAC ≥400
6%

All-cause mortality rate
11.50

11.25
12.11
17.39

2.45
2.70
2.53
4.97

21%
24%
21%
28%

19%
17%
15%
14%

60%
59%
64%
58%

6.85
6.67
7.71
10.04

Grandhi, G.R. et al. J Am Coll Cardiol Img. 2020;13(5):1175–86.
low mortality rates in follow-up duration extending beyond 12 years.

Our study was the first to document the association of CAC with CVD and CHD mortality, which might be considered more relevant outcomes to assess risk prediction compared with all-cause mortality. Across RF burden, 40% and 24% of deaths were due to CVD and CHD causes, respectively, among participants with CAC of ≥400, whereas 80% of deaths among those with CAC of 0 were attributable to non-CVD causes. Stronger association of CAC with CVD and/or CHD mortality, compared with all-cause mortality, challenges the exclusive use of traditional RFs for cardiovascular risk assessment to determine the intensity of primary prevention strategies.

**HIGH BURDEN OF TRADITIONAL RFs AND CAC OF 0.**

The absence of CAC conferred low risk for CVD events and all-cause mortality across the range of RF burden, which was shown in a meta-analysis and in large prospective studies during 5 years of follow-up (12,18,19). Blaha et al. (20) showed that nearly one-half of the individuals who met eligibility for statin therapy based on the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study criteria had CAC of 0 and experienced an extremely low event rate, with an unfavorable estimated number needed to treat for 1 CHD event.

Power of zero has gained significant importance over the past few years, especially among high-risk individuals based on the burden of traditional RFs. Nasir et al. (11), in a retrospective study of predominantly white and middle-aged asymptomatic individuals, reported that approximately one-third of study participants with ≥3 RFs had CAC of 0 and a low all-cause mortality rate of 2.72 deaths per 1,000 person-years among them over mean follow-up of 5.6 years. Silverman et al. (7) validated these findings in prospective MESA cohort that showed 35% had CAC of 0 among high-risk individuals (≥3 RFs) and a CHD event rate of 3.1 events per 1,000 person-years over a mean follow-up of 7.1 years. These findings were confirmed by

---

**TABLE 3** HRs for Mortality With Increasing CAC Score Across Increasing RF Burden in CAC Consortium

|                      | 0 RF (n = 11,428) (17%) | 1 RF (n = 23,726) (36%) | 2 RFs (n = 21,276) (32%) | ≥3 RFs (n = 10,206) (15%) |
|----------------------|------------------------|-------------------------|--------------------------|--------------------------|
| All-cause mortality  | 397 (3.47)             | 945 (3.98)              | 1,038 (4.88)             | 778 (7.62)               |
| CAC 1–100 vs. 0     | 1.06 (0.80–1.40)        | 1.15 (0.96–1.39)        | 1.31 (1.08–1.59)         | 1.32 (1.01–1.73)         |
| CAC 100–400 vs. 0   | 1.45 (1.05–1.98)        | 1.59 (1.29–1.95)        | 1.61 (1.31–1.99)         | 1.88 (1.44–2.47)         |
| CAC ≥400 vs. 0      | 1.84 (1.32–2.56)        | 2.18 (1.76–2.69)        | 2.45 (1.99–3.01)         | 3.25 (2.51–4.23)         |
| Non-CVD mortality   | 295 (2.58)              | 678 (2.86)              | 730 (3.43)               | 484 (4.74)               |
| CAC 1–100 vs. 0     | 1.04 (0.76–1.43)        | 1.09 (0.88–1.35)        | 1.32 (1.06–1.65)         | 1.27 (0.93–1.75)         |
| CAC 100–400 vs. 0   | 1.31 (0.91–1.89)        | 1.45 (1.14–1.85)        | 1.57 (1.22–2.00)         | 1.48 (1.06–2.06)         |
| CAC ≥400 vs. 0      | 1.34 (0.89–2.02)        | 1.61 (1.23–2.09)        | 2.15 (1.67–2.77)         | 2.53 (1.83–3.48)         |
| CVD mortality       | 102 (0.89)              | 267 (1.13)              | 308 (1.45)               | 294 (2.88)               |
| CAC 1–100 vs. 0     | 1.25 (0.65–2.43)        | 1.51 (1.00–2.29)        | 1.33 (0.89–1.98)         | 1.54 (0.91–2.60)         |
| CAC 100–400 vs. 0   | 2.27 (1.08–4.77)        | 2.28 (1.47–3.56)        | 1.85 (1.22–2.80)         | 3.09 (1.87–5.11)         |
| CAC ≥400 vs. 0      | 4.04 (1.89–8.64)        | 4.33 (2.77–6.79)        | 3.12 (2.06–4.72)         | 4.99 (3.03–8.24)         |
| CHD mortality       | 53 (0.46)               | 139 (0.59)              | 158 (0.74)               | 175 (1.71)               |
| CAC 1–100 vs. 0     | 1.06 (0.40–2.84)        | 1.43 (0.79–2.58)        | 1.53 (0.83–2.82)         | 1.72 (0.74–3.98)         |
| CAC 100–400 vs. 0   | 2.90 (1.08–7.75)        | 2.06 (1.09–3.91)        | 2.37 (1.26–4.43)         | 4.62 (2.10–10.19)        |
| CAC ≥400 vs. 0      | 3.87 (1.35–11.05)       | 4.64 (2.47–8.71)        | 4.35 (2.34–8.09)         | 8.47 (3.83–18.75)        |

Values are n (%) or HR (95% CI). *Model adjusted for age and sex.

Abbreviations as in Tables 1 and 2.

---

**CENTRAL ILLUSTRATION** Continued

(A) Mortality rate (per 1,000 person-years) of participants with a coronary artery calcium (CAC) score of 0 according to the burden of risk factors (RFs) in the CAC Consortium. The proportion of each type of mortality is given within the segment, and the mortality rates are given adjacent to the respective segment of the pie chart. Across the RF burden, the all-cause mortality rates were very low and most deaths were secondary to noncardiovascular disease (CVD). (B) Mortality rate (per 1,000 person-years) of individuals with CAC ≥400 according to the burden of RF in CAC Consortium. The proportion of each type of mortality is given within the segment and the mortality rates are given adjacent to the respective segment of the pie chart. Across the RF burden, the all-cause mortality rates were high and nearly 40% of the deaths were secondary to CVD.
strategy could enable focusing on individuals who are potentially deferring the use of costly pharmacotherapies. Such a strategy could enable focusing on individuals who are at a high risk to develop disease instead on those who might have been misclassified as high risk by RF burden alone, because truly high-risk individuals are most likely to benefit from more aggressive preventive therapies.

**ABSENCE OF TRADITIONAL RFs AND ELEVATED CAC.** Although CAC of 0 is an excellent prognostic indicator, high CAC scores are equally useful in identifying high-risk individuals among those with no RF. Nasir et al. (11), in a predominantly white and middle-aged population, demonstrated that 43% of the participants were at low risk due to the absence of any underlying RFs. Within this subgroup, 48% had detectable CAC and 6% had CAC >400. These low-risk individuals, with detectable CAC were at a significantly higher risk for mortality, and the all-cause mortality rate was 16.89 per 1,000 person-years among individuals with CAC >400. These findings were validated by Silverman et al. (7) in the prospective MESA cohort; in those without RFs, 32% and 5% had CAC >0 and CAC >300, respectively, and 8.9 CHD events per 1,000 person-years were noted among those with CAC >300. These findings were further validated by Kavousi et al. (23) in a meta-analysis of 5 population-based studies that showed that among asymptomatic low-risk women (10-year ASCVD risk <7.5%), CAC was present in 36%. Individuals with CAC >100 had the highest annual event rate of 9.68 events per 1,000 person-years and those with CAC 1 to 100 had 3.07 per 1,000 person-years.

### Table 4: HRs* for Mortality With Increasing RF Burden Across Increasing CAC Score

| CAC       | All-cause mortality | CVD mortality | CHD mortality |
|-----------|---------------------|---------------|--------------|
| 0         | (n = 29,757) (44%)  | (n = 7,278) (11%) |
| 1 RF vs. 0| 1.03 (0.82-1.30)    | 1.02 (0.80-1.29) |
| 2 RFs vs. 0| 1.05 (0.83-1.33)  | 1.01 (0.78-1.30) |
| ≥3 RFs vs. 0| 1.30 (0.98-1.73) | 1.28 (0.98-1.67) |
| Non-CVD mortality | 474 (1.59) | 592 (2.88) |
| 1 RF vs. 0| 1.02 (0.80-1.31)    | 0.98 (0.76-1.27) |
| 2 RFs vs. 0 | 0.98 (0.75-1.27) | 0.97 (0.72-1.31) |
| ≥3 RFs vs. 0| 1.18 (0.85-1.63) | 1.21 (0.91-1.62) |
| CVD mortality | 121 (0.41) | 0.20 (0.24) |
| 1 RF vs. 0| 1.10 (0.64-1.90)    | 1.27 (0.78-2.06) |
| 2 RFs vs. 0 | 1.44 (0.82-2.52) | 1.47 (0.91-2.39) |
| ≥3 RFs vs. 0| 1.93 (1.01-3.68) | 2.06 (1.23-3.43) |
| CHD mortality | 51 (0.17) | 90 (0.44) |
| 1 RF vs. 0| 1.23 (0.54-2.80)    | 1.50 (0.71-3.16) |
| 2 RFs vs. 0 | 1.30 (0.54-3.12) | 1.73 (0.82-3.64) |
| ≥3 RFs vs. 0| 1.66 (0.61-4.51) | 2.31 (1.06-5.07) |

Values are n (%) or HR (95% CI). *Model adjusted for age and sex.
Abbreviations as in Tables 1 and 2.
person-years compare with those with CAC of 0 (1.41 per 1,000 person-years).

Our results were consistent with these studies and able to extend them by providing cause-specific mortality information. In our study, 17% (n = 11,428) of the participants did not have RFs, and among them, 44% had CAC >0 and 6% had CAC ≥400. Participants with CAC >0 had a higher annual all-cause mortality, of which >40% and >20% of deaths were due to CVD and CHD causes, respectively. We demonstrated a significantly elevated CHD mortality rate of 2.45 deaths per 1,000 person-years among the CAC ≥400 subgroup with 0 RFs, which was nearly 7-fold of all participants with 0 RFs (0.37 per 1,000 person-years). This further challenged the exclusive use of traditional RFs for ASCVD risk estimation.

In addition, we demonstrated that CAC was also associated with non-CVD mortality, which was consistent with studies that showed CAC to be associated with non-CVDs such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, and hip fractures (24). Although CAC is unlikely to be causally associated with non-CVDs, these findings support the hypothesis of CAC to be a marker of an individual’s overall health and disease burden, including non-CVDs and associated mortality.

**STUDY LIMITATIONS.** There was a potential for referral bias, and the study sample did not represent a random sample of the population because all the participants were referred by a physician for CAC scanning based on clinical factors. We did not have data on incidental findings or subsequent treatment of patients after CAC scoring, which might affect the natural history of CHD and CVD. However, treatment of higher risk patients with preventive medications would tend to bias our prognostic results toward the null. Due to limitations inherent in vital status ascertainment in the United States, the CAC Consortium might have underestimated mortality by up to 30%, although this would be nondifferential across the CAC and/or RF groups. Another potential weakness included recall bias from self-reporting of RF information. However, Hoff et al. (25) showed a good reliability of self-reported histories of CHD RFs in self-referred individuals for electron beam computed tomography screening. However, because these individuals were self-reported as binary variables, potential residual confounding could not be ruled out, thus possibly diminishing the strength of association of RFs with mortality.

**CONCLUSIONS**

Our study added the value of CAC testing to the current published data, for a larger cohort of participants over a longer follow-up time, by demonstrating a greater proportion of total deaths due to CVD and CHD causes, as well as a significantly higher incremental risk, especially for CVD and CHD mortality with increasing CAC scores. Our study also underscored data for the power of zero, with most deaths considered non-CVD in nature in this extended follow-up in absence of CAC. Whether the proposed paradigm shift in CVD risk assessment and subsequent management decisions based on CAC detection for risk prediction and traditional RFs for targeted risk factor modification will result in more appropriate allocation of resources and improved outcomes needs to be addressed in future randomized studies.

**ADDRESS FOR CORRESPONDENCE:** Dr. Khurram Nasir, Division of Cardiovascular Prevention and Wellness, Houston Methodist DeBakey Heart & Vascular Center & Center for Outcomes Research Houston Methodist, 6550 Fannin Street, Suite 1801, Houston, Texas 77030. E-mail: knasir@houstonmethodist.org.

**PERSPECTIVES**

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** CAC significantly improves risk prediction above and beyond conventional RFs and appropriately identifies many individuals at high and low risk for ASCVD based on conventional RFs that are considered low and high risk, respectively.

**TRANSLATIONAL OUTLOOK:** Individuals with CAC of 0 at an extremely low CVD and CHD mortality rate, despite high RF burden, may be able to safely defer preventive pharmacotherapy.

**REFERENCES**

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017;135:e146-603.

2. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935-59.

3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/JAHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/
ASCVD Risk Prediction by CAC and Risk Factors

Grandhi et al.

JACC: CARDIOVASCULAR IMAGING, VOL. 13, NO. 5, 2020

MAY 2020:1175–86

1. Grandhi B, Blaha MJ, Budoff MJ, et al. Coronary artery calcium and traditional risk factors: derivation in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart J 2009;158:554–61.
2. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011;378:684–92.
3. Joshi PH, Nasir K. Discordance between risk factors and coronary artery calcium: implications for guiding treatment strategies in primary prevention settings. Prog Cardiovasc Dis 2015;58:10–8.
4. Blaha MJ, Blumenthal RS, Budoff MJ, Nasir K. Understanding the utility of zero coronary calcium as a prognostic test: a Bayesian approach. Circ Cardiovasc Qual Outcomes 2011;4:253–6.
5. Kavousi M, Desai CS, Ayers C, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. JAMA 2016;316:2126–34.
6. Handy CE, Desai CS, Dardari ZA, et al. The association of coronary artery calcium with non-cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol 2016;69:568–76.
7. Hoff JA, Davgilus ML, Chomka EV, Kralnik AJ, Svrkurov A, Kondos GT. Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30,908 healthy individuals. Ann Epidemiol 2003;13:163–9.

KEY WORDS coronary artery calcium, mortal, risk factors

APPENDIX For supplemental figures and a table, please see the online version of this paper.
The value of risk factors (RF) may reside more in determining the targets of intensive therapy in those with increased risk, rather than in factoring them into an equation that performs suboptimally in determining that risk. Once risk is established, either by clinical disease in secondary prevention or by coronary artery calcium (CAC) defined subclinical disease in primary prevention, aggressive attention should be directed to modifying those factors that are modifiable\(^{(1)}\). This mandate, published in 2004, is echoed in the study by Grandhi et al. \(^{(2)}\) in this issue of \textit{iJACC} in the concluding statement of the Interplay of Coronary Artery Calcium and Risk Factors for Predicting cardiovascular disease [CVD]/coronary heart disease [CHD] Mortality: The CAC Consortium: “Whether the proposed paradigm shift in CVD risk assessment and subsequent management decisions based on CAC detection for risk prediction and traditional RFs for targeted risk factor modification will result in more appropriate allocation of resources and improve outcomes need to be addressed in future randomized studies.”

In their study of the CAC Consortium multicenter cohort of 66,636 primary prevention patients followed for a median of 12.5 years who underwent CAC scanning, the authors uniquely evaluated cause-specific mortality (CHD, CVD, and non-CVD, as well as all-cause mortality) instead of the universally applied all-cause mortality alone of previous studies. There were 3,158 (4.7%) deaths, of which 32% were the result of CVD and 68% of non-CVD causes. Compared with 0 CAC, CAC $\geq 400$ was associated with a hazard ratio of 5.44 (95% confidence interval [CI]: 3.88 to 7.62) and 4.15 (95% CI: 3.29 to 5.22) for CHD and CVD mortality as opposed to hazard ratios of 2.09 (95% CI: 1.52 to 2.85) and 1.84 (95% CI: 1.46 to 2.31), respectively, for $\geq 3$ risk factors compared with 0 RF. CAC added prognostic value at every RF level, particularly highlighted in 0 CAC individuals by mortality rates per 1,000 patient-years of 1.42 to 2.25 (all-cause), 0.24 to 0.56 (CVD), 0.10 to 0.22 (CHD), and 1.18 to 1.69 (non-CVD) across 0 to $\geq 3$ RFs, compared with mortality rates in those with $\geq 3$ RF and increasing CAC from 0 to $> 400$ of 2.2 to 17.39 (all cause), 0.56 to 7.34 (CVD), 2.2 to 4.97 (CHD), and 1.69 to 10.04 (non-CVD). In addition, there was a greater proportion of deaths from CVD and CHD with increasing CAC irrespective of RFs \(^{(2)}\).

As the authors acknowledge, their results mirror those of other reports, with the added virtues of the cause-specific data, which should assuage critics who are not content with all-cause mortality alone, and long follow-up. Their report adds to the remarkably consistent mass of CAC data confirming its superiority to RF, and the erroneous allocation of treatment based on RF alone. For example, of the Multiethnic Study of Atherosclerosis participants for whom the American College of Cardiology/American Heart Association cholesterol management guidelines would recommend moderate to high-intensity statins on the basis of their $\geq 7.5\%$ 10-year risk by the pooled cohort equation (PCE) \(^{(3)}\), 41% had 0 calcium scores. Of the 12% to be considered for moderate intensity statins on the basis of their 5% to $<7.5\%$ 10-year risk, 57% had 0 CAC. In the $<5\%$ 10-year risk group for whom statins were not recommended, 17% had CAC of 1 to 100 and 4% had CAC $>100$ \(^{(4)}\).
How then, is the unequivocal superiority of CAC to RFs incorporated into the latest prevention guidelines (5,6)?

“Class I: For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of [atherosclerotic CVD] ASCVD by using the pooled [PCE].

Class IIA: In adults at intermediate risk (>7.5% to <20% 10-year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10-year ASCVD risk), if risk-based decisions for preventive interventions (e.g., statin therapy) remain uncertain, it is reasonable to measure a coronary artery calcium score to guide clinician–patient risk discussion” as illustrated in Figure 1.

Clearly, CAC plays a more important role than in past guideline iterations and has regained its Class IIA classification. Moreover, it is the first guideline-recommended management decision paradigm based on CAC risk groups. Just as clearly, however, it has retained its second-class status. If CAC is superior to RFs, why begin the risk assessment process with a RF based PCE? The Grandhi et al. (2) call for randomized controlled trials demonstrating CAC mediated improvement in outcomes is concordant with sound scientific methodology but is it really necessary in the setting of a risk assessment tool that is so superior to risk factors, as reported by Grandhi et al. (2)? No risk factor–based assessment has ever been validated by a randomized trial, yet the PCE remains the initial step in the paradigm. If neither CAC nor the PCE have randomized trials, isn’t it obvious that the more powerful tool should be the first step? A randomized controlled trial, although desirable, should not be necessary to prove that aggressive treatment of patients at high risk identified by CAC screening will improve outcomes or that avoiding statin treatment in patients in the lowest risk 0 CAC category, for whom statin benefit has never been demonstrated, will not be harmful. Why restrict CAC for use only after patient or clinical uncertainty emerges in the shared decision-making process? What, exactly, does clinical uncertainty mean? How can we be sure that there will be shared decision making and that CAC will even be discussed during shared decision making, if it does occur? It is unlikely to be raised as an alternative by the patient and it would be naive to assume that physicians will take the initiative.
What is the alternative? Are we now entering the controversial realm of CAC screening of the entire population? The US Preventive Services Task Force has consistently rejected this alternative, most recently in 2018: “There are insufficient adequately powered clinical trials evaluating the incremental effect of the [ankle-brachial index, high-sensitivity C-reactive protein] level, or CAC score in risk assessment and initiation of preventive therapy. Furthermore, the clinical meaning of improvements in measures of calibration, discrimination, and reclassification risk prediction studies is uncertain” (7).

Because it is evident that CAC will not gain population-based screening approval without randomized trials, it is appropriate to narrow its application to treating individual patients, which, after all, is the essence of the practice of medicine.

All patients, as part of the requisite shared decision making, should be informed of the possibility of improved risk assessment by CAC and given the option of this evaluation as the first step of the prevention paradigm (Figure 2).

For the 5% to <20% 10-year risk patients, the only change from the existing guideline is to move shared decision making to the beginning of the evaluation process and to expand it to include a CAC discussion irrespective of patient indecision or clinical uncertainty. The >20% 10-year risk group should be treated as per the 2018 Cholesterol Practice Guidelines (5) but for those who are intolerant of statins, or wish to discontinue or not begin statins or PCSK9 inhibitors, CAC may be used to persuade them of the importance of drug adherence if the high risk is confirmed or reassure them of low 5-year risk if CAC = 0 (8).

Because events do occur in patients with 0% to 4% 10-year risk, it is reasonable to offer concerned patients further reassurance if CAC = 0 or appropriate treatment if subclinical atherosclerosis is present.

Naturally, radiation exposure, scan costs, and incidentalomas are potential concerns, as well as denying the option of CAC to those who cannot afford the test. These same objections have been considered and dismissed for the 5% to <20% 10-year risk group who are already included in the guideline. Insurance coverage for this increasingly inexpensive test would be extremely helpful but is still, for the most part, unavailable.

In this era of patient-centered imaging and shared decision making, it is unacceptable for the public, and
physicians as well, to be unaware of and not have the option of using the best test for identification of their cardiac risk, as Grandhi et al. (2) have elegantly demonstrated. Yes, it is time to change the Cholesterol Clinical Practice Guidelines. Again!

ADDRESS FOR CORRESPONDENCE: Dr. Harvey S. Hecht, Mount Sinai Saint Luke’s Medical Center, 1111 Amsterdam Avenue, New York, New York 10025. E-mail: harvey.hecht@mountsinai.org.

REFERENCES

1. Hecht HS. Atherosclerotic risk factors revisited. Am J Cardiol 2004;93:73–5.
2. Grandhi GR, Mirbolouk M, Dardari ZA, et al. Interplay of coronary artery calcium and risk factors for predicting CVD/CHD mortality: the CAC consortium. J Am Coll Cardiol Img 2020;13:1175–86.
3. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935–59.
4. Khurram Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association Cholesterol Management Guidelines. MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2015;66:1657–68.
5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.
6. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease. A Special Report From the American Heart Association and American College of Cardiology. J Am Coll Cardiol 2019;74:3153–67.
7. U.S. Preventive Services Task Force. Risk assessment for cardiovascular disease with nontraditional risk factors: US Preventive Services Task Force recommendation statement. JAMA 2018;320:272–80.
8. Valenti V, Hartaigh Bo, Heo R, et al. A 15-year warranty period for asymptomatic individuals without coronary artery calcium. A prospective follow-up of 9,715 individuals. J Am Coll Cardiol Img 2015;8:900–9.

KEYWORDS coronary artery calcium, mortality, risk factors
Diagnostic Accuracy of FDG PET/CT in Suspected LVAD Infections
A Case Series, Systematic Review, and Meta-Analysis

Marty C. Tam, MD, Vaibhav N. Patel, MD, Richard L. Weinberg, MD, PhD, Edward A. Hulten, MD, MPH, Keith D. Aaronson, MD, MS, Francis D. Pagani, MD, PhD, James R. Corbett, MD, Venkatesh L. Murthy, MD, PhD

ABSTRACT

OBJECTIVES The purpose of this study was to describe our experience with fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography computed tomography (PET/CT) in diagnosing left ventricular assist device (LVAD) infections and perform a meta-analysis of published studies to determine overall diagnostic accuracy.

BACKGROUND Device-related infections are a common complication of LVADs and are linked to worse outcomes. Diagnosis of LVAD infections remains challenging. FDG PET/CT has demonstrated good diagnostic accuracy in several other infectious conditions.

METHODS This was a single-center, retrospective case series of FDG PET/CT scans in suspected LVAD infection between September 2015 and February 2018. A systematic review of PubMed from database inception through March 2018 was also conducted to identify additional studies.

RESULTS Nineteen FDG PET/CT scans were identified for the retrospective case series. The systematic review identified an additional 3 publications, for a total of 4 studies involving 119 scans assessing diagnostic performance. Axial (n = 36) and centrifugal (n = 83) flow LVADs were represented. Pooled sensitivity was 92% (95% confidence interval [CI]: 82% to 97%) and specificity was 83% (95% CI: 24% to 99%) for FDG PET/CT in diagnosing LVAD infections. Summary receiver-operating characteristic curve analysis demonstrated an AUC of 0.94 (95% CI: 0.91 to 0.95).

CONCLUSIONS FDG PET/CT for suspected LVAD infections demonstrates good diagnostic accuracy, with overall high sensitivity but variable specificity. (J Am Coll Cardiol Img 2020;13:1191-202) © 2020 by the American College of Cardiology Foundation.
Durable left ventricular assist devices (LVADs) are an important therapeutic option in the management of end-stage heart failure, with approximately 3,500 new device implants per year in the United States (1,2). Among the most common LVAD complications are device-related infections, occurring at a rate of 13.6 per 100 patient-months during the first 3 months post-implant and 4.6 per 100 patient-months thereafter. The presence of an LVAD infection carries increased morbidity and mortality (1).

Unfortunately, although some definitions and diagnostic approaches for LVAD infections have been published, use and implementation remain challenging (3,4). LVAD-specific infections can be classified into pump and cannula, pump pocket, and superficial and deep driveline infections. Diagnostic confidence is enhanced by assessing multiple major and minor criteria that integrate clinical, microbiologic, and histologic criteria (Supplemental Table 1). Standard work-up of suspected LVAD infections include a complete blood count, chest radiography, and 3 sets of blood cultures over a 24-h period. If there is suspicion for pump or driveline infections, gram stain and culture of the site is recommended. Additionally, other potential sources of infection should be considered. In some cases, erythrocyte sedimentation rate and C-reactive protein may have value. Transthoracic echocardiography and transesophageal echocardiography (TEE), ultrasoundography, computed tomography (CT), and tagged white blood cell scans may also be useful depending on clinical circumstances.

Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography computed tomography (PET/CT) is a sensitive, specific, and accurate test for the diagnosis of infection, including infections of cardiac implantable electronic devices and prosthetic valves (5–9). Although case reports and series have described FDG PET/CT findings in patients with LVADs, these studies are few in number (10–21). Furthermore, no systematic reviews exist specifically assessing FDG PET/CT use in the LVAD population. As such, no practice guidelines for use in suspected LVAD infections exist.

We sought to describe our experience with FDG PET/CT for the diagnosis of possible LVAD infections and systematically review the published reports regarding the diagnostic accuracy of FDG PET/CT scanning for suspected device infections in the LVAD population.

**METHODS**

**CASE SERIES.** Selection. This single-center case series is a retrospective study of consecutive FDG PET/CT scans performed on LVAD patients between September 2015 and February 2018 at the University of Michigan. Studies were identified through screening all cardiac FDG PET/CT scans protocol to assess for inflammation in this time frame. Inclusion criterion was LVAD device at the time of scan. Exclusion criterion was scan not performed to assess for possible infection. Demographic data as well as pertinent history, laboratory values, imaging studies and clinical outcomes were obtained from medical record review. Possible, probable, or proven LVAD-specific infections (Supplemental Table 1) were grouped together as having a clinicandetermined device-specific infection and served as a reference standard for diagnostic testing. These determinations were based on provider assessment during the initial care encounter and confirmed on 30-day follow-up.

This study was approved by the Institutional Review Board at the University of Michigan and waiver of informed consent was granted for this retrospective case series.

**FDG PET/CT protocol.** A standardized protocol at the University of Michigan was used for inflammatory cardiac PET studies. Patients were instructed to maintain a high-fat, low-carbohydrate, protein-permitted diet for all meals beginning with breakfast on the day before the FDG PET/CT scan. On the morning of the study, after an overnight fast, patients underwent rubidium-82 PET/CT resting perfusion imaging to help delineate myocardial borders. Immediately after perfusion imaging, patients were given a high fat drink. After a minimum of 3 h, patients were injected with 8 to 10 mCi of FDG. Three boluses of 10 units/kg of unfractionated heparin were injected at 15-min intervals beginning 10 min before FDG injection. In some cases, the perfusion scan was performed the day before FDG PET for scheduling reasons. Approximately 1 h after FDG injection, patients underwent PET/CT imaging (Siemens mCT-64, Siemens Medical Imaging, Knoxville, Tennessee) including cardiac gating. When necessary, additional bed positions were acquired to cover the entire LVAD system and any other cardiac devices. In cases where clinical suspicion warranted, whole-body imaging was also performed. Attenuation corrected and non-attenuation corrected images were obtained. Physicians interpreting the studies were not blinded to clinical data.
**TABLE 1** Baseline Case Series Patient Data

|                       | Total (N = 19) | No LVAD Infection (n = 8) | LVAD Infection (n = 11) | p Value |
|-----------------------|----------------|---------------------------|-------------------------|---------|
| Age, yrs              |               |                           |                         |         |
| 61.0 (50, 65)         | 63.0 (61.5, 68.0) | 56.0 (45.0, 59.0)         | 0.013*                  |         |
| Female                | 4 (21.1)       | 3 (37.5)                  | 1 (9.1)                 | 0.26    |
| Ethnicity             | 0.34           |                           |                         |         |
| African American      | 5 (26.3)       | 1 (12.5)                  | 4 (36.4)                |         |
| Caucasian             | 14 (73.7)      | 7 (87.5)                  | 7 (63.6)                |         |
| Etiology of heart failure | 0.32         |                           |                         |         |
| Cardiac sarcoidosis   | 2 (10.5)       | 1 (12.5)                  | 1 (9.1)                 |         |
| Ischemic              | 9 (47.4)       | 3 (37.5)                  | 6 (54.5)                |         |
| Mixed ischemic/nonischemic | 2 (10.5) | 0 (0.0)                   | 2 (18.2)                |         |
| Nonischemic           | 5 (26.3)       | 4 (50.0)                  | 1 (9.1)                 |         |
| Familial/viral        | 1 (5.3)        | 0 (0.0)                   | 1 (9.1)                 |         |
| Type of LVAD          | 0.63           |                           |                         |         |
| Axial flow pump       | 7 (36.8)       | 2 (25.0)                  | 5 (45.5)                |         |
| Centrifugal flow pump | 12 (63.2)      | 6 (75.0)                  | 6 (54.6)                |         |
| LVAD indication       | 0.67           |                           |                         |         |
| Bridge to candidacy    | 1 (5.3)        | 0 (0.0)                   | 1 (9.1)                 |         |
| Bridge to decision    | 3 (15.8)       | 2 (25.0)                  | 1 (9.1)                 |         |
| Bridge to transplant  | 7 (36.8)       | 2 (25.0)                  | 5 (45.5)                |         |
| Destination therapy   | 8 (42.1)       | 4 (50.0)                  | 4 (36.4)                |         |
| LVAD implant to FDG PET/CT time, days | 59.0 (189, 1,234) | 584.5 (479.5, 1,357.5) | 309.0 (105, 1,234) | 0.32 |
| Prosthetic valve      | 11 (57.9)      | 4 (50.0)                  | 7 (63.6)                | 0.66    |
| Cardiac electronic implantable device | 18 (94.7) | 8 (100)                  | 10 (90.9) | 1.00 |
| Diabetes              | 10 (52.6)      | 3 (37.5)                  | 7 (63.6)                | 0.37    |
| Insulin use           | 6 (31.6)       | 2 (25.0)                  | 4 (33.3)                | 1.00    |
| White blood cell count, K/µl | 13.10 (7.70, 19.60) | 12.50 (8.70, 17.35) | 13.10 (6.6, 23.7) | 0.51 |
| Erythrocyte sedimentation rate, MM | 28.5 (19.0, 44.0) | 28.0 (23, 29) | 44.0 (19, 78) | 0.35 |
| C-reactive protein, mg/dl | 3.65 (1.50, 8.40) | 1.50 (1.5, 7.9) | 3.70 (3.6, 8.4) | 0.60 |
| Lactate dehydrogenase, IU/l | 340.0 (259.0, 381.0) | 363.0 (259.0, 376.5) | 319.0 (259, 441) | 0.90 |
| Insulin level at time of scan, µIU/ml | 21.40 (13.20, 32.90) | 13.80 (11.9, 28.65) | 22.70 (16.9, 34.3) | 0.19 |
| C-peptide at time of scan, ng/ml | 5.5 (4.4, 6.9) | 5.1 (4.0, 7.2) | 5.5 (4.6, 6.9) | 0.74 |
| Glucose at time of scan, mg/dl | 111.0 (86.0, 143.0) | 106.5 (88.5, 126) | 118.0 (86, 147) | 0.59 |
| Triglycerides at time of scan, mg/dl | 140 (114, 229) | 146 (132.5, 278.5) | 136 (113, 229) | 0.51 |
| Free fatty acid at time of scan, mmol/l | 1.090 (0.98, 1.300) | 1.120 (1.015, 1.36) | 1.090 (0.94, 1.30) | 0.87 |

Values are n (%) or median (interquartile range [25th, 75th]). *Significance with alpha level of < 0.05 between no infection and infection group.

FDG PET/CT = fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; LVAD = left ventricular assist device.

**SYSTEMATIC REVIEW. Selection.** This systematic review and meta-analysis was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement guidelines (23). A PubMed search was performed for all publications that included the use of FDG PET/CT in diagnosing suspected LVAD infections, from database inception through March 2018 (Supplemental Appendix). After duplicate search results were removed, all abstracts were independently assessed by 2 reviewers (M.C.T., V.N.P.) for the desired diagnostic test and patient population. Full-text reviews of screened studies were assessed for inclusion and exclusion criteria. Single-patient case reports and studies that did not report test characteristics (i.e., sensitivity and specificity) were excluded. All but the most recent publication for a given center’s database were excluded. The reference lists of the selected articles were also screened for suitable publications.

**Data extraction.** Data extraction was performed independently by 2 reviewers (M.C.T., V.N.P.), with any differences reconciled by mutual agreement. Information on study size, number of PET scans, type of LVAD, age, time from implantation, use of attenuation correction, and treatment for LVAD infection was collected. The principle measure obtained was results of PET scans defined as true positive, true negative, false positive, or false negative using a reference standard of clinician-determined final diagnosis.

**Quality of evidence.** Risk of bias was assessed by 2 reviewers (M.C.T., V.N.P.) using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool (24), with any differences reconciled by mutual agreement.
DATA ANALYSIS AND META-ANALYSIS. Demographic and clinical data were assessed by standard descriptive statistics for comparison groups. Continuous variables were described as median (interquartile range) and between-group differences were tested for statistical significance with Mann-Whitney U tests. Categorical variables were described as frequencies, and between-group differences were tested with Fisher exact tests. All statistical tests were 2-sided with a 0.05 significance level. Clinician-determined possible, probable, or proven LVAD-specific infection were grouped together for analysis. For the case series, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were determined. For the meta-analysis, extracted data were used to determine pooled sensitivity, specificity, and summary receiver-operating characteristic (SROC) curves with area under the curve (AUC). A generalized linear mixed model approach for diagnostic test accuracy using random effects (25) was used with meta-analysis commands (26). Study heterogeneity was assessed by Higgins I² (27). Publication bias was assessed by Deeks’ funnel plot (28). Analyses were performed with Stata version 13.0 (StataCorp, College Station, Texas).

RESULTS

CASE SERIES. Overall, 20 FDG PET/CT scans assessing for inflammation in LVAD patients were performed between September 2015 and February 2018. One scan was excluded because it was ordered to assess sarcoidosis activity and not infection. Therefore, 19 scans performed on 18 patients were included for analysis. One patient had 2 scans for separate care episodes. LVAD devices studied include axial (n = 7) and centrifugal (n = 12) continuous-flow pumps.

Baseline data for the groups with (n = 11) and without (n = 8) LVAD infections are shown in Table 1. As statistically significant differences were noted with respect to age (p = 0.013). No differences were noted between the remaining demographic and history characteristics. Importantly, no between group differences were noted in traditional infectious markers.

![True Positive Scan](image)
A 33-year-old man with a centrifugal flow left ventricular assist device who presented with fatigue and fevers, and subsequently was found to have Streptococcus anginosus bacteremia. Note the increased radiolabeled uptake along the device pump (red arrows) and tricuspid valve ring (yellow arrows), indicating high metabolic activity and possible infection. The patient was treated for device infection with intravenous antibiotics for 6 weeks and then suppressive therapy.
such as white blood cell count, erythrocyte sedimentation rate, and C-reactive protein. There were also no differences seen in markers of adequate study preparation including insulin level, C-peptide, serum glucose, triglycerides, and free fatty acid.

Patient-level clinical data for the nineteen scans were collected (Supplemental Table 2). Compared with clinician-determined presence or absence of LVAD infection, FDG PET/CT scanning produced 11 true positives, 2 true negatives, 6 false positives, and 0 false negatives. Figures 1 to 3 highlight examples of these scans. Of the 11 true positive scans, 6 cases were treated with antibiotics alone, 1 required LVAD exchange, 2 underwent eventual heart transplantation, 2 died, and 1 had a concurrent uterine abscess. Of the 2 true negatives, 1 had cholecystitis (Figure 2) and 1 was treated empirically with antibiotics without a clear source of infection. Of the 6 false positives, 1 received antibiotics for an empyema, 1 had a cardiac implantable electronic device extracted for infection and eventual unrelated heart transplantation, 1 had an aortic endograft infection, 1 had concomitant active cardiac sarcoidosis requiring steroids, 1 had no clear source of infection but nonspecific uptake along mitral and tricuspid prostheses and treated empirically with antibiotics, and 1 was newly diagnosed with chronic myeloid leukemia (Figure 3).

At our center, FDG PET/CT for diagnosing LVAD infections had 100% (95% confidence interval [CI]: 72% to 100%) sensitivity and 25% (95% CI: 3.1% to 65%) specificity, with a positive likelihood ratio of 1.33 (95% CI: 0.89 to 2.00) and a negative likelihood ratio of 0.00.

TEE scans were obtained in 10 of the cases (6 true positive, 1 true negative, and 3 false positive FDG PET/CT scans). None demonstrated definitive intracardiac vegetations, with only 1 scan demonstrating a likely Lambl’s excrescence. CT scans were obtained in 12 of the cases (7 true positive, 2 true negative, and 3 false positive FDG PET/CT scans). In patients treated as an LVAD infection, CT scans were suggestive of LVAD infection in 2 of 7 cases. In patients not treated as an LVAD infection, none of the 5 CT scans
showed evidence of LVAD infection, though they did point to other sources of infection in 2 cases.

**SYSTEMATIC REVIEW. Selection.** There were 57 publications identified through the PubMed search, with no duplicates (Figure 4). All abstracts were screened, and 45 studies were excluded because they did not involve both FDG PET/CT testing and the LVAD patient population. Full-text review of the remaining 12 articles was completed, with an additional 9 articles excluded. Of these 9 publications, 4 were single-patient reports, 2 were older publications (14,16) from an overlapping dataset of a more recent publication (18), and 3 did not include information about diagnostic test characteristics (12,20,21). Notably, large studies by Kanapinn et al. (20) assessing utility of quantitative changes in serial FDG PET/CT scans in 30 nonconsecutive LVAD patients and Kim et al. (21) assessing clinical outcomes related to location of FDG uptake in 35 consecutive LVAD patients were excluded because the studies were not designed to assess the accuracy of FDG PET/CT for LVAD infections.

**Quality of evidence.** The QUADAS-2 analysis (Supplemental Table 3) showed overall low risk for bias for patient selection, unclear risk for bias for index test and flow or timing, and high risk of bias for reference standard. The high risk for bias with the reference standard domain is due to lack of a true gold standard test for diagnosing LVAD infections. There is overall low concern for applicability in all domains.

**Study characteristics and outcomes.** Included publications are summarized in Table 2, totaling 119 FDG PET/CT scans. Axial flow (n = 36) and centrifugal flow (n = 83) LVAD scans were represented in this group. Median time from LVAD implant to FDG PET/CT scan in the studies varied from 134 to 559 days. Overall, there were 6 false negatives, 12 false positive, 32 true negative, and 69 true positive scans. All but 1 study (15) commented on use of both nonattenuation and attenuation corrected images. Treatments and outcomes of for patients with LVAD infections included prolonged antibiotics (n = 11), surgical exploration or device exchange (n = 18), heart transplant (n = 29), and death (n = 14).
META-ANALYSIS. Figure 5 shows the forest plots of individual study sensitivity and specificity. Pooled sensitivity was 92% (95% CI: 82% to 97%) and specificity was 83% (95% CI: 24% to 99%) for FDG PET/CT in diagnosing LVAD infections. SROC analysis demonstrates an AUC of 0.94 (95% CI: 0.91 to 0.95) (Central Illustration).

Heterogeneity between studies as assessed by the Higgins I² statistic was 0.00% (95% CI: 0.00% to 100.0%) for sensitivity and 80.71% (95% CI: 62.08% to 99.33%) for specificity (Figure 5). Publication bias was assessed with a Deeks’ funnel plot (p = 0.82) (Supplemental Figure 1).

DISCUSSION

DIAGNOSTIC VALUE OF FDG PET/CT IN LVAD INFECTIONS. This is the first systematic review and meta-analysis assessing the diagnostic accuracy of FDG PET/CT in LVAD infections. Overall, FDG PET/CT performed well despite a limited number of studies. There was a high diagnostic accuracy, with a SROC curve AUC of 0.94, indicating a potential expanded role for this imaging technology in assessing suspected LVAD infections. Of interest, there was a notably high sensitivity based on this case series (100%) and the meta-analysis (92%), suggesting that this modality may be particularly useful in ruling-out infections when there is a low to intermediate pre-test probability. Specificity was lower for the case series (25%), though it was higher in the meta-analysis (83%) with wide CIs. This suggests less usefulness for ruling in infections. Overall, this meta-analysis assessed LVAD patients with a wide range of baseline characteristics, enhancing generalizability.
**Factors Influencing Diagnostic Value of FDG PET/CT in LVAD Infections.** Inflammatory cells have increased glucose metabolism and concentrate FDG. Therefore, increased FDG uptake in PET/CT scanning is seen in noninfectious inflammatory conditions as well, such as postoperative states, myocarditis, and sarcoidosis (29,30). Patient factors such as time from LVAD implant and etiology of heart failure need to be taken into consideration when interpreting the results of these scans. Normal myocytes also utilize glucose as a metabolic substrate. In the absence of adequate patient metabolic preparation before FDG PET/CT scanning, normal cardiac myocytes can concentrate FDG, which can alter test specificity. Careful metabolic preparation needs to be taken to drive myocytes toward fatty acid, rather than glucose, metabolism to suppress any background FDG uptake in the myocardium. Levels of insulin, C-peptide, serum glucose, triglycerides, and free fatty acid were measured in this case series to assess for adequate metabolic preparation. No significant differences were noted between groups, suggesting no difference in metabolic preparation between groups studied in this case series.

Of note, this case series includes 6 false positive scans, with 4 having concurrent bacteremia or other possible sources of infection, 1 having concurrent increased cardiac sarcoidosis activity, and 1 having a new diagnosis of chronic myeloid leukemia. It remains unclear if these concurrent infectious and inflammatory conditions play a role in the increased FDG uptake near the components of the LVAD but could contribute to false positive scans.

Antibiotic use before the imaging may also play a role in attenuating the degree of FDG uptake in areas of infection. This has the potential for increasing the rates of false negatives and reducing test sensitivity. While it is unclear the exact impact of antibiotic use and duration on the results of testing, rates of false negatives remained low, at 5.0% (6 of 119 scans) in this meta-analysis, and pooled sensitivity remained high.

Attenuation correction is used to enhance image quality and allow for better quantification of FDG uptake in PET/CT scans, but also can produce artifacts around metallic material such as an LVAD due to overcorrection for attenuation and subsequent overestimation of FDG PET/CT activity (31). This is a source of false positive studies, though FDG uptake around metallic objects should be confirmed on nonattenuation corrected images as they are less prone to manifest the same artifact. Protocols for interpretation of FDG PET/CT studies in the LVAD population should include review of the nonattenuation corrected images for this reason.

Study heterogeneity as determined by the Higgins I² statistic for diagnostic testing is not an absolute measure, but increasing values indicate increasing...
likelihood of heterogeneity (32,33). For the studies included in the meta-analysis, heterogeneity was low with respect to sensitivity ($I^2 = 0.00\%$), but given the wide CI, the significance is unclear. With respect to specificity ($I^2 = 80.71\%$), heterogeneity was high. Although this may reflect random chance, methodology errors, or study design differences, there is likely a component of a threshold effect. Sensitivity and specificity are linked variables that change inversely based on the threshold for relative FDG uptake. Currently no universally accepted standard has been set, which may limit the current utility of this testing. The limited number of studies also leads to an underpowered analysis.

**INTEGRATING FDG PET/CT WITH OTHER CLINICAL DATA IN DIAGNOSING LVAD INFECTIONS.** Suspected LVAD infections can be difficult to diagnose and often require integrating clinical and testing data (3,4). As noted in this case series, traditional blood biomarkers of infection (Table 1) and imaging with TEE and CT (Supplemental Table 2) were poor predictors for LVAD infection when viewed as standalone tests, further highlighting the need for a combined approach. FDG PET/CT can significantly add to current practice given the high diagnostic accuracy (AUC: 0.94) and pooled sensitivity (92%) found in this meta-analysis. Making an accurate diagnosis in this setting is important given the increased mortality with LVAD infections and the implications of subsequent therapy (prolonged antimicrobial therapy, LVAD exchange, heart transplant).

A proposed algorithm for incorporating FDG PET/CT testing is outlined here. For all patients with suspected LVAD infection, usual work-up includes a pertinent history and physical, blood biomarkers for infection, blood cultures, wound cultures if purulence is present at the driveline exit site, chest radiograph, and additional imaging if there is suspicion for a pump or intracardiac infection (thoracic echocardiography with possible TEE, ultrasonography, or CT of the chest or abdomen). Based on this initial clinical information, cases of proven LVAD infection can proceed to appropriate treatment without further testing and cases of unlikely device infection should prompt a search for an alternate diagnosis. In the remaining cases where there is diagnostic uncertainty and risks of surgical exploration are high, then FDG PET/CT may be obtained. Positive results would indicate need for treatment of a LVAD infection and negative scans would indicate an alternate diagnosis. In some situations, incidental FDG uptake can be seen in non-LVAD components, leading to appropriate therapy for a different diagnosis.

**STUDY LIMITATIONS.** For the case series, a limitation is the small sample size, which is not necessarily powered to detect difference in the baseline characteristics described. Therefore, the significance of
certain markers in assessing for LVAD infections may be underestimated. For the meta-analysis, sensitivity analyses including tests of heterogeneity and publication bias are also underpowered with the number of studies included.

With the systematic review and meta-analysis, 1 limitation is the variation in dietary or metabolic preparation and imaging protocols used by different centers, which can alter the accuracy of testing. This likely contributed to the study heterogeneity. For our cases series, the dietary preparation used aligns with current data for effective myocardial suppression (22).

In general, selection bias is also important to consider. It is unlikely that all patients with suspected LVAD infections receive FDG PET/CT scans, leading to potential errors in assessing diagnostic accuracy. Similarly, no patients were evaluated who did not have suspected infection.

The lack of a true reference standard test for diagnosing LVAD infections also poses a major limitation in cases where no surgeries are performed or when surgical specimens at time of device explant are not feasible. Therefore, the diagnosis of infection relies on several clinical, laboratory, and imaging factors, which may lead to errors in determining the true diagnostic accuracy of any single test or imaging modality. Furthermore, for the cases included in the systematic review, interpretation of FDG PET/CT was not necessarily blinded from other clinical data and may have influenced the outcome of the scan.
Finally, the retrospective nature of this study also leads to potential confounding variables that may have affected the results. Further prospective studies are needed to address these issues.

CONCLUSIONS

In this case series and systematic review with meta-analysis of all pertinent studies on the use of FDG PET/CT in diagnosing LVAD infections, FDG PET/CT demonstrated good diagnostic accuracy, with overall high sensitivity but variable specificity.

ADDRESS FOR CORRESPONDENCE: Dr. Marty C. Tam, Division of Cardiovascular Medicine, Department of Medicine, University of Michigan, 1500 East Medical Center Drive, 2381 CVC, Ann Arbor, Michigan 48109-5873. E-mail: mctam@med.umich.edu.

REFERENCES

1. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080-6.
2. Liang Q, Ward S, Pagani FD, et al. Linkage of Medicare records to the interagency registry of mechanically assisted circulatory support. Ann Thorac Surg 2018;105:1397-402.
3. Hannan MM, Husain S, Mattner F, et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transplant 2011;30:375-84.
4. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 2013;32:157-87.
5. Juneau D, Golfam M, Haza S, et al. Positron emission tomography and single-photon emission computed tomography imaging in the diagnosis of cardiac implantable electronic device infection: a systematic review and meta-analysis. Circ Cardiovasc Imaging 2017;10:e005772.
6. Yan J, Zhang C, Niu Y, et al. The role of 18F-FDG PET/CT in infectious endocarditis: a systematic review and meta-analysis. Int J Clin Pharmacol Ther 2016;54:337-42.
7. Mahmood M, Kendi AT, Ajmal S, et al. Meta-analysis of 18F-FDG PET/CT in the diagnosis of infective endocarditis. J Nucl Cardiol 2019;26:922-35.
8. Mahmood M, Kendi AT, Farid S, et al. Role of 18F-FDG PET/CT in the diagnosis of cardiovascular implantable electronic device infections: a meta-analysis. J Nucl Cardiol 2019;26:958-70.
9. Juneau D, Golfam M, Haza S, et al. Molecular imaging for the diagnosis of infective endocarditis: a systematic literature review and meta-analysis. Int J Cardiol 2018;253:183-8.
10. Costa S, Houna E, Massetti M, Belin A, Bouvard G, Agostini D. Impact of F-18 FDG PET-CT for the diagnosis and management of infection in JARVIK 2000 device. Clin Nucl Med 2011;36:e188-91.
11. Tili G, Picard F, Pinay J-B, Dominguez-Dossantos P, Bordeneuve L. The usefulness of FDG PET/CT imaging in suspicion of LVAD infection. J Nucl Cardiol 2014;21:845-8.
12. Kim J, Feller ED, Chen W, Dilsizian V. FDG PET/CT Imaging for LVAD Associated Infections. J Am Coll Cardiol Img 2014;7:839-42.
13. Fujino T, Higo T, Tanoue Y, Ide T. FDG-PET/CT for driveline infection in a patient with implantable left ventricular assist device. Eur Heart J Cardiovasc Imaging 2016;17:23.
14. Dell’Aquila AM, Mastrobuoni S, Alles S, et al. Contributory role of fluorine 18-fluorodeoxyglucose positron emission tomography/computed tomography in the diagnosis and clinical management of infections in patients supported with a continuous-flow left ventricular assist device. Ann Thorac Surg 2016;101:87-94; discussion 94.
15. Bernhardt AM, Panirasad MA, Brand C, et al. The value of fluorine-18 deoxyglucose positron emission tomography scans in patients with ventricular assist device specific infections. Eur J Cardiother 2017;51:1072-7.
16. Avramovic N, Dell’Aquila AM, Weckesser M, et al. Metabolic volume performs better than SUVmax in the detection of left ventricular assist device driveline infection. Eur J Nucl Med Mol Imaging 2017;44:1870-7.
17. Dejust S, Guedec-Ghelare E, Blanc-Autrant E, et al. Fluorine-18 F-FDG PET/CT Imaging of Infection in Implanted Electronic Device Detection and Follow-Up. J Nucl Med 2017;58:948-54.
18. Dell’Aquila AM, Avramovic N, Mastrobuoni S, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography for improving diagnosis of infection in patients on CF-LVAD: Lingoing for more “insights.” Eur Heart J Cardiovasc Imaging 2018;19:632-43.
19. Akin S, Muslem R, Constantinescu AA, et al. 18F-FDG PET/CT in the diagnosis and management of continuous flow left ventricular assist device infections: a case series and review of the literature. ASAIO J 1992;18:411-9.
20. Kanapim P, Burchett W, Körperich H, Körfer J. 18 F-FDG PET/CT-imaging of left ventricular assist device infection: a retrospective quantitative intrapatient analysis. J Nucl Cardiol 2018 Jan 16 [E-pub ahead of print].
21. Kim J, Feller ED, Chen W, Liang Y, Dilsizian V. FDG PET/CT for Early Detection and Localization of Left Ventricular Assist Device Infection: Impact on Patient Management and Outcome. J Am Coll Cardiol Img 2019;12:722-9.
22. Osborne MT, Hulten EA, Murthy VL, et al. Patient preparation for cardiac fluorine-18 fluorodeoxyglucose positron emission tomography imaging of inflammation. J Nucl Cardiol 2017;24:86-99.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9. W64.
24. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
25. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. J Clin Epidemiol 2006;59:1312-3. author reply 1312-3.
26. Owamena B. MIDAS: Stata module for meta-analytical integration of diagnostic test accuracy studies. 2009. Available at: https://ideas.repec.}

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Assessing for suspected infection with FDG PET/CT scanning has significant clinical implications for the management of LVAD patients, given that making the diagnosis is challenging. Integration of FDG PET/CT into the current diagnostic algorithm provides an accurate and sensitive test of infection.

TRANSLATIONAL OUTLOOK: Current practices for assessing suspected LVAD infections vary and advanced imaging such as FDG PET/CT scan should be considered. Diagnostic accuracy and sensitivity of this test is high, but future studies should focus on improving the specificity of the test to have even greater clinical importance.
org/c/boc/bocode/s456880.html. Accessed April 9, 2018.

27. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.

28. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882-93.

29. Garg G, Benchekroun MT, Abraham T. FDG-PET/CT in the postoperative period: utility, expected findings, complications, and pitfalls. Semin Nucl Med 2017;47:579-94.

30. Kircher M, Lapa C. Novel noninvasive nuclear medicine imaging techniques for cardiac inflammation. Curr Cardiovasc Imaging Rep 2017;10:6.

31. Sureshbabu W, Mawlawi O. PET/CT imaging artifacts. J Nucl Med Technol. 2005;33:156-61. quiz 163-4.

32. Lee J, Kim KW, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers-part ii. statistical methods of meta-analysis. Korean J Radiol 2015;16:1188-96.

33. Borenstein M, Higgins JPT, Hedges LV, Rothstein HR. Basics of meta-analysis: I2 is not an absolute measure of heterogeneity: Res Synth Methods 2017;8:5-18.

KEY WORDS diagnostic testing, heart failure, infection, left ventricular assist device, meta-analysis, positron emission tomography

APPENDIX For an expanded Methods section as well as supplemental tables and a figure, please see the online version of this paper.
Advances in tackling the progressive nature of heart failure have improved prognosis for many, yet a select few transition into the state of advanced heart failure. This condition, heralded by intolerance to neurohormonal directed pharmacological therapy, is associated with a poor quality of life, recurrent need for hospitalization, and a large toll of deaths due to ventricular pump failure (1). In this circumstance, only a biological approach of cardiac transplantation or use of mechanical therapy involving implantation of left ventricular assist devices (LVADs) effectively prolong quality-adjusted life-years (2). Disruptive engineering has provided us with mechanical support devices that ameliorate hemocompatibility-related adverse events such as stroke, pump thrombosis, and bleeding, but have not successfully addressed the vexing dilemma of device related infection, a persistent cause of significant morbidity (3,4). The propensity for infection appears obvious because current generation LVADs require a driveline that breaks the skin surface barrier and exits the abdominal wall to attach to a console that provides power transmission to the internal pump.

However, the predilection for infection with a LVAD is not as simple an issue as a break in a sterile skin barrier. Curiously, it has been observed that unique immunological changes occur as the circulation is confronted with the foreign device that induces T cells to activation-induced cell death and progressive defects in cellular immunity with a consequent increase in fungal infections (5). Investigations have confirmed that suppressive T regulatory cells emerge in an LVAD-supported circulation and compromise cellular immunity, which in turn leads to infection that is more systemic than just localized to the device (6). Therefore, it is no surprise that serious infections are observed in over one-half of all patients supported with contemporary LVADs at 24 months, and only a little over a third of these infections involve the driveline of the pump (4). Thus, diagnosing the exact origin, location, and extent of infections in those with an LVAD implant is of immense relevance in guiding therapy.

Recognizing this heterogeneity, the International Society for Heart and Lung Transplantation developed a classification system to catalogue infection into device-specific, device-related, or nondevice infection (7). The diagnostic journey to define and classify these infections requires a structured approach to initially include system-level diagnosis (infection biomarkers, blood and urine cultures, and radiography), and then attention shifts to a more device specific diagnosis to look “near” and “within” the device. Sometimes a driveline-related infection is clear, when suppuration is present or simple imaging such as ultrasonography and a computerized scan successfully outline the presence of a fluid collection accessible for aspiration and analysis. Even then, whether a deeper extension of the infection exists remains an occasional dilemma. In other cases, spread of infection to other coexisting biomaterial (central catheters, pacemaker or defibrillator leads), to surgical site infection (mediastinitis), or within the components of the pump housing need to be clearly defined. Clinicians pursue any number of tests to sort these issues, principal among which are anatomical imaging modalities such as echocardiography (transthoracic and transesophageal), ultrasonography to diagnose abscess, or computerized tomography for localization.

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Heart and Vascular Center, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts. Dr. Mehra has received consulting fees from Abbott (paid to Brigham and Women’s Hospital), Medtronic, Janssen, Mesoblast, Portola, Bayer, Xogenex, NupulseCV, FineHeart, and the Baim Institute for Clinical Research. Dr. Woolley has received consulting fees from Abbott.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.
Others rely on more functional imaging tests such as indium-labeled leukocyte scans. These separate tests lack sufficient sensitivity or specificity in making a definitive diagnosis. In this context, positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (18F-FDG PET/CT) has emerged as a powerful imaging tool, given its ability to simultaneously provide both anatomical and physiological assessments. Specifically, the advantages of using 18F-FDG PET/CT imaging over other imaging modalities include the ability to map the extent of the infection, identify tissue sites or location of the infection, and assess the temporal response to treatment. This imaging technique has been used in a wide array of infections such as prosthetic valve endocarditis, septic joint prostheses, and fever of unknown origin (8,9). One major limitation of this technique is the lack of discrimination between infection or inflammation, and this issue becomes critical in assessing implanted hardware, such as ventricular assist devices.

In this issue of iJACC, Tam et al. (10) report a retrospective, single-center case series of 18F-FDG PET/CT scans performed in a small cohort of 18 patients suspected to have a LVAD-associated infection between September 2015 and February 2018 and they go on to develop a systematic review using a meta-analysis of studies published through March 2018. Interestingly they include their series along with 3 additional studies and provide an aggregate view of the accuracy of this technique in a total of 119 scans for assessment. Although the investigators demonstrate a high negative predictive value for the use of 18F-FDG PET/CT (92%), they also lay bare the poor specificity, which ranged widely from 25% to 83% in their analysis. The reasons for this include the lack of experience in interpretation and absence of a standard-bearer tool, as a greater burden of evidence is necessary to move this to the forefront as a routine modality in our diagnostic and therapeutic armamentarium, but it may be carefully utilized in select clinical conditions.

REFERENCES

1. Kalogeropoulos AP, Samman-Tahan A, Hedley JS, et al. Progression to stage D heart failure among outpatients with stage C heart failure and reduced ejection fraction. J Am Coll Cardiol HF 2017;5:528–37.
2. Mehra MR. Evolving disruption in left ventricular assist systems: forgiving but not yet forgettable. Eur J Heart Fail 2019;21:98–100.
3. Mehra MR. The burden of haemocompatibility with left ventricular assist systems: a complex weave. Eur Heart J 2019;40:673–7.
4. Mehra MR, Urieil N, Naka Y, et al., MOMENTUM 3 investigators. A fully magnetically levitated left ventricular assist device - final report. N Engl J Med 2019;380:1618–27.
5. Ankersmit HJ, Tugulea S, Spanier T, et al. Activation-induced T-cell death and immune dysfunction after implantation of left-ventricular assist device. Lancet 1999;354:550–5.
6. Kimball PM, Flattery M, McDougan F, Kasrjan V. Cellular immunity impaired among patients on left ventricular assist device for 6 months. Ann Thorac Surg 2008;85:1566–61.
7. Hassan MM, Husain S, Mattner F, et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transplant 2011;30:375–84.
8. Granados U, Fuster D, Péricas J, et al., Hospital Clinic Endocarditis Study Group. Diagnostic accuracy of 18F-FDG PET/CT in infective endocarditis and implantable cardiac electronic device infection: a cross-sectional study. J Nucl Med 2016;57:1726–32.
9. Bharucha T, Rutherford A, Slooch S, Alavi A, Brown M, Galloway J. FDG-PET/CT in fever of unknown origin working group. Diagnostic yield of
FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise. Clin Radiol 2017;72:764–71.

10. Tam MC, Patel VN, Weinberg RL, et al. Diagnostic accuracy of FDG PET/CT in suspected LVAD infections: a case series, systematic review, and meta-analysis. J Am Coll Cardiol Img 2020;13:1191-202.

11. Shao D, Tian XW, Gao Q, Liang CH, Wang SX. Preparation methods prior to PET/CT scanning that decrease uptake of 18F-FDG by myocardium, brown adipose tissue, and skeletal muscle. Acta Radiol 2017;58:10–8.

12. Padera RF. Infection in ventricular assist devices: the role of biofilm. Cardiovasc Pathol 2006;15:264–70.

13. Verberne SJ, Rajmakers PG, Temmerman OP. The accuracy of imaging techniques in the assessment of periprosthetic hip infection: a systematic review and meta-analysis. J Bone Joint Surg Am 2016;98:1638–45.

KEY WORDS diagnosis, heart failure, infection, LVAD, PET/CT scan
Heterogeneity of Plaque Structural Stress Is Increased in Plaques Leading to MACE
Insights From the PROSPECT Study

Charis Costopoulos, MD, PhD,a Akiko Maehara, MD,b Yuan Huang, PhD,c,d,e Adam J. Brown, MD, PhD,a Jonathan H. Gillard, MD,c Zhongzhao Teng, PhD,d,e Gregg W. Stone, MD,b Martin R. Bennett, MD, PhDc

ABSTRACT

OBJECTIVES This study sought to determine if plaque structural stress (PSS) and other plaque stress parameters are increased in plaques that cause future major adverse cardiovascular event(s) (MACE) and if incorporating these parameters improves predictive capability of intravascular ultrasonography (IVUS).

BACKGROUND Less than 10% of coronary plaques identified as high-risk by intravascular imaging result in subsequent MACE. Thus, more specific measurements of plaque vulnerability are required for effective risk stratification.

METHODS Propensity score matching in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study plaque cohort resulted in 35 nonculprit lesions (NCL) associated with future MACE and 66 matched NCL that remained clinically silent. PSS was calculated by finite element analysis as the mechanical loading within the plaque structure in the periluminal region.

RESULTS PSS was increased in the minimal luminal area (MLA) regions of NCL MACE versus no MACE plaques for all plaques (PSS: 112.1 ± 5.5 kPa vs. 90.4 ± 3.3 kPa, respectively; p = 0.001) and virtual histology thin-cap fibroatheromas (VH-TCFAs) (PSS: 119.2 ± 6.6 kPa vs. 95.8 ± 5.0 kPa, respectively; p = 0.005). However, PSS was heterogeneous over short segments, and PSS heterogeneity index (HI) was markedly greater in NCL MACE than in no-MACE VH-TCFAs (HI: 0.43 ± 0.05 vs. 0.29 ± 0.03, respectively; p = 0.01). Inclusion of PSS in plaque assessment improved the identification of NCLs that led to MACE, including in VH-TCFAs (p = 0.03) and plaques with MLA ≤4 mm² (p = 0.03). Incorporation of an HI further improved the ability of PSS to identify MACE NCLs in a variety of plaque subtypes including VH-TCFA (p = 0.001) and plaques with MLA ≤4 mm² (p = 0.002).

CONCLUSIONS PSS and variations in PSS are increased in the peri-MLA regions of plaques that lead to MACE. Moreover, longitudinal heterogeneity in PSS is markedly increased in MACE plaques, especially VH-TCFAs, potentially predisposing to plaque rupture. Incorporation of PSS and heterogeneity in PSS may improve the ability of IVUS to predict MACE. (J Am Coll Cardiol Img 2020;13:1206–18) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Cardiovascular disease is a leading cause of mortality worldwide (1), and most deaths are attributable to ischemic heart disease. Techniques that can identify coronary plaques at risk for adverse events are therefore of particular interest. Virtual histology intravascular ultrasonography (VH-IVUS) can determine both plaque size and composition, resulting in an imaging-based plaque classification. PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), the largest VH-IVUS study to date, showed that minimal luminal area (MLA) ≤ 4.0 mm², plaque burden (PB) ≥ 70% at the MLA, and the presence of virtual histology thin-cap fibroatheroma (VH-TCFA) were independent predictors of nonculprit (NCL) future major adverse cardiovascular event(s) (MACE) over a 3-year period (2). In contrast, NCL nonfibroatheromas were rarely associated with MACE over the same interval (3). Subsequently both the VIVA (VH-IVUS in vulnerable atherosclerosis) and the AtheroRemoIVUS (European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis-Intravascular Ultrasound Study; NCT01789411) studies found that VH-TCFA and PB ≥ 70% were associated with future events (4,5). Although the consistency of all 3 prospective studies validates these features to identify higher risk plaques, <10% of NCL VH-TCFAs led to MACE in all 3 studies, indicating that more specific techniques are required to better characterize coronary plaques.

Plaque structural stress (PSS) is the stress located inside an atherosclerotic plaque due to plaque structure and composition, and is affected by vessel expansion and stretch induced by arterial pressure. PSS is linked to plaque rupture both ex and in vivo (6,7), so incorporation of PSS into coronary plaque assessment may improve the ability of imaging to identify high-risk coronary plaques. Indeed, PSS is increased in culprit plaques of patients presenting with acute coronary syndrome (ACS) versus stable angina (8) and in the peri-MLA region of those showing rupture versus no rupture (9). PSS was increased in NCL MACE plaques in the VIVA study compared to no-MACE plaques with similar gray-scale and VH-IVUS characteristics (10). However, for plaque stress measurements to be useful clinically they need to be validated in larger multi-center studies, and other stress-based parameters may be more predictive of MACE than PSS alone. The current study aimed to determine if a) PSS of plaques responsible for NCL MACE in PROSPECT are increased compared to a propensity-score-matched control population; b) if other stress-based parameters were more discriminatory; and (c) if incorporating different PSS parameters provides incremental prognostic information over IVUS imaging alone.

**METHODS**

**PATIENT RECRUITMENT.** The protocol for the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study and inclusion and exclusion criteria have already been described (2) (Supplemental Appendix). Briefly, 697 patients with ACS were recruited across 37 U.S. and European sites after undergoing successful percutaneous coronary intervention for all coronary lesions responsible for the index event and completion of any other planned interventions. A total of 623 patients underwent 3-vessel gray-scale and VH-IVUS assessment, and medication therapy after discharge was followed according to guideline standards. Clinical follow-up occurred at 30 days, 6 months, and annually for at least 2 years (median: 3.4 years).

**VH-IVUS IMAGE ACQUISITION AND ANALYSIS.** VH-IVUS was performed in the left main stem and proximal 6 to 8 cm of the major epicardial vessels using a 20-MHz synthetic aperture array 3.2-F catheter (Eagle Eye, In-Vision Gold, Volcano, Rancho Cordova, California) with motorized catheter pull back (0.5 mm/s) after the administration of glycerin trinitrate. A plaque was defined as ≥3 consecutive frames with PB ≥ 40% and classified as VH-TCFA, thick-cap fibroatheroma (VH-ThCFA), pathological intimal thickening (VH-PIT), fibrotic (VH-FT), or fibrocalcific plaque (VH-FCa). The MLA was defined as the IVUS frame with the smallest luminal area over the whole plaque. A lesion was classified as having PB ≥ 70% if PB at the MLA site was ≥ 70%. Analysis

---

**ABBREVIATIONS AND ACRONYMS**

- **FEA** = finite element analysis
- **HI** = heterogeneity index
- **MACE** = major adverse cardiovascular event(s)
- **MLA** = minimal luminal area
- **PB** = plaque burden
- **PSS** = plaque structural stress
- **VH-IVUS** = virtual histology intravascular ultrasonography
- **VH-TCFA** = virtual histology thin-cap fibroatheroma

---

received royalties through Columbia University from Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

Manuscript received October 4, 2018; revised manuscript received April 17, 2019, accepted May 3, 2019.
was performed off-line and was not used for procedural guidance.

**Clinical Endpoints and Definitions.** Independent study monitors verified all data for case report forms. The pre-specified primary endpoint was the incidence of MACE defined as the composite of cardiac death, cardiac arrest, myocardial infarction, or hospitalization due to unstable or progressive angina according to Braunwald unstable angina classification and the Canadian Cardiovascular Society angina classification. The primary endpoint was adjudicated by a clinical events committee that had no knowledge of other patient data. Clinical events were attributed to culprit lesions or non-culprit lesions (NCL) based on follow-up angiography. If angiography was not performed, the event was classified as indeterminate.

**Biomechanical Analysis.** Vessel geometry and plaque composition were extracted from radio-frequency IVUS data and imported into dedicated analysis software (proprietary code, MATLAB R2012b, MathWorks, Inc, Natick, Massachusetts), allowing construction of 8,182 VH-IVUS models. Briefly, each VH-IVUS frame was segmented into its individual components using an in-house MATLAB code with the resulting segmented model undergoing dynamic 2D FEA simulations as described previously (Supplemental Appendix). A 65-μm layer of fibrous tissue was introduced during mesh generation to account for the limited axial resolution of VH-IVUS to detect a fibrous cap between lumen and necrotic core/dense calcium. Maximum principal stress was used to indicate the critical mechanical conditions, the PSS, with variations in PSS being the difference between PSS in systole and that in diastole. As plaque destabilization is a focal event, PSS across the whole plaque may not reflect PSS where plaque disruption occurs. Therefore, PSS and variations in PSS in the peri-MLA segments (±4 mm proximal and distal to the MLA with PB ≥40%) were compared, as this represents extensive disease and where plaque disruption often occurs (9). The heterogeneity of PSS along the length of each plaque was also examined as this can amplify the effects of PSS or variations in PSS at areas of fibrous cap weakness thereby promoting

---

**Figure 1 Patient and Plaque Populations**

Schematic representation of patient and plaque populations included in the study. MACE = major adverse cardiovascular event(s); NCL = non-culprit lesion; PB = plaque burden; VH-IVUS = virtual histology intravascular ultrasonography.

---

If a patient has multiple NCLs:
1. Choose NCL with MACE
2. If multiple NCL MACE in patients with multiple NCLs with PB ≥60%, choose NCL associated with the first NCL MACE
3. If multiple NCLs without MACE, choose the NCL with the greatest PB

---

1:2 Propensity score matching

35 NCLs with MACE

66 NCLs without MACE

37 patients/lesions

155 patients/2142 lesions

582 lesions

65 lesions

21 lesions

35 NCLs with MACE related to NCLs that were not identified at baseline or without valid VH-IVUS data were eliminated from the analysis

Patients with gray-scale IVUS (3229 NCLs in 660 patients)

Non-culprit lesions with PB ≥60% (1087 lesions in 505 patients)

Candidate NCLs with MACE

Candidate NCLs without MACE

35 NCLs with MACE

66 NCLs without MACE

1208 Costopoulos et al. PSS and Future Clinical Events in the PROSPECT Study

JACC: CARDIOVASCULAR IMAGING, VOL. 13, NO. 5, 2020 MAY 2020:1206–18

Schematic representation of patient and plaque populations included in the study. MACE = major adverse cardiovascular event(s); NCL = non-culprit lesion; PB = plaque burden; VH-IVUS = virtual histology intravascular ultrasonography.
plaque rupture. This was assessed by the heterogeneity index (HI), defined as the standard deviation of PSS divided by mean PSS or variations in PSS in the area of interest.

**STATISTICAL ANALYSIS.** Propensity score matching with a 1:2 ratio was used to identify NCL MACE and no-MACE groups to minimize selection bias due to differences in patient and lesion characteristics. Only 1 lesion per patient was selected, and only those patients with a PB $\geq 60\%$ at the MLA were included, because more than 85% of NCL MACE occurred in lesions with a PB $\geq 60\%$. In patients with multiple NCL, the lesion with the greatest PB was chosen. However, PSS was also calculated for all VH-IVUS frames with PB $\geq 40\%$. Both patient and lesion parameters were used in calculation of propensity scores. Patient-level parameters included presence of insulin-treated diabetes mellitus, history of percutaneous coronary intervention, age, and sex. Lesion-level parameters included PB at the MLA, MLA, and plaque classification (Supplemental Appendix). Propensity score matching generated 101 NCLs, 35 of which led to future MACE (Figure 1). The remaining 66 NCLs formed the control group. The C-statistic was 0.887, and the Hosmer-Lemeshow test p value was 0.931, confirming good discrimination and goodness-of-fit of the propensity score model. A total of 8,182 VH-IVUS frames were analyzed with a median of 66 (42 to 104) frames per plaque.

Data variables are median (quartile [Q]1 to Q3) and were compared using the Mann-Whitney U test. As each plaque had multiple VH-IVUS slices, a linear mixed-effects model was used to compare groups by using a random effect for plaque and fixed effects for group to account for clustering with results presented as mean $\pm$ SEM. All calculations were 2-tailed and a p value $<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curves were calculated by plotting sensitivity versus (1-specificity), allowing calculation of the area under the curve (AUC) and the identification of PSS and heterogeneity in PSS cutoff thresholds that best predicted future MACE. Each cutoff value was subsequently applied to categorize PSS and heterogeneity in PSS into low and high groups, allowing generation of time-to-event curves that incorporated these. Time-to-event data are presented as Kaplan-Meier estimates of cumulative hazard and were compared using the log-rank method. Statistical analyses were performed using both SPSS version 19.0.0 software (IBM, Armonk, New York) and R version 2.10.1 software (R Foundation for Statistical Computing, Vienna, Austria).

### RESULTS

**BASELINE PATIENT CHARACTERISTICS.** A total of 101 patients were included in the analysis, 35 of whom experienced a NCL MACE. Patient demographics were similar between the 2 groups (Supplemental Table 1). There were no significant differences in rates of diabetes (28.6% vs. 19.7%, respectively; p = 0.31) or hypercholesterolemia (53.6% vs. 49.2%, respectively; p = 0.70). Initial clinical presentation was also similar between the MACE and no-MACE groups, with most patients presenting with non-ST-segment elevation myocardial infarction (68.6% vs. 72.7%, respectively; p = 0.66). Following treatment of culprit vessels, patients began medical therapy according to local guidelines. There were no significant differences between the 2 groups for antplatelet, statin, angiotensin-converting enzyme inhibitor, or beta-blocker therapy, either at discharge or follow-up (Supplemental Table 2).

**BASELINE NONCULPRIT LESION ANGIOGRAPHIC AND IVUS CHARACTERISTICS.** Vessels of patients underwent quantitative angiographic coronary and IVUS analysis. There were no significant differences in the number of diseased vessels, defined as diameter of stenosis on quantitative angiographic coronary analysis $>30\%$, or number of vessels with lesions (Supplemental Table 3). Gray-scale IVUS analysis revealed some differences between the 2 groups.

#### TABLE 1 VH-IVUS Characteristics of MACE and No MACE Nonculprit Lesions

| Lesion phenotype | MACE (n = 35) | No MACE (n = 66) | p Value |
|------------------|--------------|-----------------|---------|
| VH-TCFA          | 20/35 (57.1) | 31/66 (47.0)    | 0.33    |
| VH-ThCFA         | 12/35 (34.3) | 26/66 (39.4)    | 0.61    |
| VH-PIT           | 2/35 (5.7)   | 9/66 (13.6)     | 0.32    |
| VH-FCa           | 1/35 (2.9)   | 0/66 (0.0)      | 0.35    |
| VH-FT            | 0/35 (0.0)   | 0/66 (0.0)      | NA      |
| VH-TFCa or VH-ThCFA | 32/35 (91.4) | 57/66 (86.4)    | 0.54    |

Plaque data

- % NC volume: 15.5 (9.0-21.5) vs. 14.9 (8.8-23.1) p = 0.73
- % DC volume: 6.1 (2.7-9.8) vs. 6.3 (3.6-9.4) p = 0.95
- % FT volume: 60.7 (54.5-65.9) vs. 57.6 (53.7-62.0) p = 0.22
- % FF volume: 15.2 (10.9-22.5) vs. 16.4 (10.2-22.2) p = 0.78

MLA site data

- % NC CSA: 13.9 (8.7-25.1) vs. 16.6 (8.9-25.1) p = 0.44
- % DC CSA: 5.0 (2.3-10.9) vs. 6.0 (2.0-11.4) p = 0.73
- % FT CSA: 61.1 (53.7-68.8) vs. 58.7 (49.0-64.2) p = 0.11
- % FF CSA: 11.1 (7.0-22.0) vs. 12.6 (5.8-22.2) p = 0.80

Values are n/N (or median (interquartile range)).

CSA = cross-sectional area; DC = dense calcification; FT = fibrofatty; FF = fibrous; MLA = minimum luminal area; NC = necrotic core; MACE = major adverse cardiovascular event(s); MLA = minimum luminal area; PIT = pathological intimal thickening; TCFA = thin-cap fibroatheroma; ThCFA = thin-cap fibroatheroma; FCa = fibrocalcific; NCL = nonculprit lesion; MLA = minimum luminal area; PIT = pathological intimal thickening; TCFA = thin-cap fibroatheroma; ThCFA = thin-cap fibroatheroma; SEM. All calculations were 2-tailed and a p value $<0.05$ was considered statistically significant.
FIGURE 2 Temporal and Longitudinal Variation in PSS

(A) VH-IVUS frame and PSS band plots in systole and in diastole. (B) Longitudinal variations of PSS in no-MACE and MACE plaques with examples of VH-IVUS images and corresponding PSS band plots. PSS = plaque structural stress; other abbreviations as in Figure 1.
Echolucent plaques were more frequent in the MACE group (34.3% vs. 12.1%, respectively; \( p = 0.008 \)) but with similar NCL length (30.4 mm [range 19.5 to 41.4 mm] vs. 24.3 mm [range 15.7 to 36.7 mm], respectively; \( p = 0.11 \)). There were no significant differences in other gray-scale IVUS characteristics (Supplemental Table 4). In both groups, virtual histology fibroatheroma was the predominant type of lesion (91.4% vs. 86.4%, respectively; \( p = 0.54 \)), approximately 50% were VH-TCFA (57.1% vs. 47.0%, respectively; \( p = 0.33 \)). There were no significant differences in overall plaque composition, defined as percent of fibrous tissue, fibrofatty tissue, necrotic core, or dense calcium, either over the whole plaque or at the MLA (Table 1).

**PSS IN NONCULPRIT LESIONS WITH MACE AT THE PERI-MLA SEGMENTS.** A total of 101 nonculprit plaques (35 with MACE, 66 with no-MACE) were
analyzed, generating 8,182 VH-IVUS frames, all of which underwent FEA to calculate mean PSS and PSS variations at systole and diastole (Figure 2A). PSS and variations in PSS across the entire plaque length were similar between the 2 groups, regardless of plaques subtype (Supplemental Figure 1). However, PSS was markedly heterogeneous across the whole plaque, even over short distances (Figure 2B), reflecting small changes in plaque composition at the luminal surface.

PSS and variations in PSS were increased in MACE compared to those in the no-MACE groups in the peri-MLA regions regardless of whether all plaques (PSS: 112.1 ± 5.5 kPa vs. 90.4 ± 3.3 kPa; p = 0.001; variations in PSS: 30.5 ± 1.5 kPa vs. 24.5 ± 0.9 kPa; p = 0.001) or only VH-TCFA plaques (PSS: 119.2 ± 6.6 kPa vs. 95.8 ± 5.0 kPa; p = 0.005; variations in PSS: 32.3 ± 1.8 kPa vs. 25.9 ± 1.4 kPa; p = 0.004) were examined (Figures 3A and 3B). PSS was also increased in MACE compared to those in no-MACE plaques with MLA ≤4 mm² (PSS: 100.3 ± 7.5 kPa vs. 83.6 ± 2.7 kPa; p = 0.007; variations in PSS: 27.5 ± 2.1 kPa vs. 22.6 ± 0.7 kPa; p = 0.007) (Figure 3C) and with PB ≥70% at the MLA site, although this was of borderline statistical significance (106.4 ± 6.7 kPa vs. 90.1 ± 5.2 kPa; p = 0.05; variations in PSS: 29.1 ± 1.9 vs. 24.4 ± 1.4 kPa; p = 0.05) (Figure 3D). PSS and variations in PSS were also increased in the MACE group when VH-TCFAs with an MLA ≤4 mm² specifically was examined (Figure 3E) but not VH-TCFA with PB ≥70% (Figure 3F).
FIGURE 5  Time-to-Event Curves for MACE Rates According to Baseline Plaque Characteristics and PSS Group

**A**
Adjusted Log-Rank = 0.002

**B**
Adjusted Log-Rank = 0.03

**C**
Adjusted Log-Rank = 0.03

**D**
Adjusted Log-Rank = 0.03

**E**
Adjusted Log-Rank = 0.12

**F**
Adjusted Log-Rank = 0.77

Cumulative MACE probability for (A) all plaques, (B) VH-TCFAs, (C) plaques with MLA ≤4 mm², (D) VH-TCFA + MLA ≤4 mm², (E) plaques with PB ≥70% at the MLA, and (F) VH-TCFA + PB ≥70% according to high or low PSS. All plaques = 101 (100%); VH-TCFA = 51 (50.5%); MLA ≤4 mm² = 47 (46.5%); VH-TCFA + MLA ≤4 mm² = 20 (19.8%); PB ≥70% at the MLA = 55 (54.5%); VH-TCFA + PB ≥70% = 21 (20.8%). Abbreviations as in Figures 1 and 3.
Heterogeneity in PSS and variations in PSS was increased at the peri-MLA segment.

Substantial differences were observed in PSS along the plaque length, even over short distances (Figure 2B, Supplemental Figure 2). Therefore the heterogeneity of PSS and variations in PSS in MACE versus no-MACE plaques were examined using a standard HI. Although heterogeneity of PSS or PSS variations in all plaques were similar between the 2 groups (PSS HI: \( p = 0.07 \); variations in PSS HI: \( p = 0.05 \)) (Figure 4A), both parameters were markedly greater in MACE VH-TCFAs (PSS HI: \( p = 0.01 \); variations in PSS HI: \( p = 0.02 \)) (Figure 4B), and in VH-TCFAs with MLA ≤4 mm² (PSS HI: \( p = 0.02 \); variations in PSS HI: \( p = 0.03 \)) (Figure 4C). Heterogeneity was similar in plaques with MLA ≤4 mm² (Figure 4D), PB ≥70% at the MLA site (Figure 4E), or VH-TCFA plus PB ≥70% (Figure 4F) in both groups.

**INTEGRATION OF PSS AND HETEROGENEITY IN PSS IMPROVED PREDICTION OF MACE.** In PROSPECT, VH-TCFAs (4.9% vs. 1.3%; \( p = 0.001 \)), plaques with MLA ≤4 mm² (5.3% vs. 1.1%; \( p = 0.001 \)), and those with PB ≥70% at the MLA site (9.6% vs. 1.2%; \( p = 0.001 \)) were more likely to lead to NCL MACE. However, 45.5% of NCL MACE plaques had an MLA >4 mm², 54.5% had PB <70% at the MLA site, and 49.0% of MACE occurred in non-VH-ThCFA plaques (2) (Supplemental Figure 3). Therefore, PSS and PSS heterogeneity were examined in an attempt to improve the ability of baseline plaque features to stratify coronary plaque risk.

ROC analysis was used first to identify the PSS and heterogeneity in PSS cutoff thresholds that best predicted future MACE (Supplemental Figure 4). Including PSS in plaque assessment markedly improved the identification of nonculprit plaques that led to MACE for all plaques (\( p = 0.002 \)) (Figure 5A), for VH-TCFAs (\( p = 0.03 \)) (Figure 5B), for plaques with MLA ≤4 mm² (\( p = 0.03 \)) (Figure 5C), or for VH-TCFA plaques with an MLA ≤4 mm² (\( p = 0.03 \)) (Figure 5D) but not plaques with PB ≥70% at the MLA (\( p = 0.12 \)) (Figure 5E) or VH-TCFA plaques with a PB ≥70% at the MLA (\( p = 0.77 \)) (Figure 5F).

Incorporating HI further improved the ability to use PSS as a means of distinguishing between MACE and no-MACE NCLs across a variety of plaque characteristics including all plaques (\( p = 0.001 \)) (Figure 6A), VH-TCFA plaques (\( p = 0.001 \)) (Figure 6B), PB ≥70% at the MLA site (\( p = 0.01 \)) (Figure 6C), MLA ≤4 mm² (\( p = 0.002 \)) (Figure 6D), and VH-TCFA plaques with an MLA ≤4 mm² (\( p = 0.004 \)) (Figure 6E) but not VH-TCFA plaques with a PB ≥70% (\( p = 0.36 \)) (Figure 6F). Further analysis demonstrated acceptable positive predictive values for high PSS and high HI across a variety of plaque subtypes (Supplemental Appendix).

**DISCUSSION**

Both post-mortem and prospective VH-IVUS studies have identified TCFA (or VH-TCAFA) as the lesion most likely to rupture (2,4,5,11). However, TCFA are frequent in patients with coronary artery disease (2,12); they are present in patients with both stable and unstable syndromes (13), and <10% actually lead to MACE within several years. Furthermore, MACE are not restricted to TCFA, suggesting that factors additional to plaque morphology are important in determining which plaques act as precursors of future events.

PSS is regulated by plaque composition, geometry, luminal configuration, and hemodynamic factors (8), and may contribute to plaque risk stratification. In the VIVA study, PSS was increased in culprit plaques of patients who presented with ACS versus those with stable angina and in those that ruptured and led to future MACE (8-10). Furthermore, the combination of PSS estimates and IVUS provided results that were superior to those of IVUS alone in identifying plaques that led to MACE. However, VIVA was a small single-center study in 170 patients without angiographic confirmation of all MACE, and such findings require confirmation in larger, multicenter cohorts. It is also unclear whether there are PSS parameters that are better discriminators of MACE than those studied in VIVA.

The present study compared a cohort with NCL MACE from the 697-patient multicenter PROSPECT study with a propensity-matched control group (8). Although PSS did not differ between the 2 groups across the entire plaque length, significant differences were observed in the peri-MLA regions, sites where plaque destabilization is most likely to occur (14) (Central Illustration). More specifically, PSS and variations in PSS were higher in MACE plaques regardless of whether all plaques, VH-TCFAs, or plaques with MLA ≤4 mm² were examined. Both parameters were also increased in NCL with PB ≥70% at the MLA, although this did not quite reach statistical significance; which is not unexpected because the propensity score matching process included only plaques with PB ≥60% at the MLA site.

High PSS in the peri-MLA segments can lead to plaque destabilization either by triggering rupture or by increasing vulnerability through necrotic core growth. Increased variations in PSS between systole and diastole may also result in fibrous cap fatigue,
Cumulative MACE probability for (A) all plaques, (B) VH-TCFAs, (C) plaques with PB $\geq 70\%$ at the MLA, (D) plaques with MLA $\leq 4\ mm^2$, (E) VH-TCFA + MLA $\leq 4\ mm^2$, and (F) VH-TCFA + PB $\geq 70\%$ according to the presence or absence of high PSS or high HI. All plaques $= 101\ (100\%);$ VH-TCFA $= 51\ (50.5\%);$ MLA $\leq 4\ mm^2 = 47\ (46.5\%);$ VH-TCFA + MLA $\leq 4\ mm^2 = 20\ (19.8\%);$ PB $\geq 70\%$ at the MLA $= 55\ (54.5\%);$ VH-TCFA + PB $\geq 70\% = 21\ (20.8\%).$ HI = heterogeneity index; other abbreviations as in Figures 1 and 3.
**CENTRAL ILLUSTRATION**

High PSS and High Heterogeneity in PSS Is Associated With Increased Risk of Future MACE in VH-TCFA

(A) VH-IVUS and its associated band plot in a VH-TCFA. (B) PSS, variations in PSS and heterogeneity index of PSS is increased in VH-TCFAs with future MACE. (C) Incorporation of PSS and heterogeneity index in PSS allows the identification of VH-TCFAs that lead to MACE.

*p < 0.05. HI = heterogeneity index; MACE = major adverse cardiovascular event(s); PSS = plaque structural stress; VH-TCFA = virtual-histology thin-cap fibroatheroma.

Costopoulos, C. et al. J Am Coll Cardiol Img. 2020;13(5):1206-18.
further promoting plaque disruption. Heterogeneity in PSS and variations in PSS in peri-MLA segments were also increased in VH-TCFAs associated with MACE versus those in no-MACE patients (Central Illustration). This could be due to subtle differences in plaque composition or luminal geometry or both, which may result in points of fibrous cap weakness in the longitudinal direction (as opposed to the axial direction, hypothesized with increased variations in PSS). Increased PSS heterogeneity in conjunction with high PSS would therefore further promote plaque destabilization.

One aim of plaque imaging is to identify the subset of plaques at highest risk of MACE, so that therapy and monitoring can be adjusted according to prognosis. This is particularly important for new treatments such as PCSK9 inhibitor therapy (15) or canakinumab therapy (16), which may be too expensive for the entire population at risk. This study found that PSS and HI calculations significantly improved plaque risk stratification, an important consideration when most plaques classified as high-risk by imaging alone remain clinically silent (Central Illustration). Indeed, there was divergence of the time-to-event curves for both PSS and heterogeneity of PSS within 1 year of follow-up (Figures 4 and 5), which further implicates PSS in plaque destabilization. As PSS, like plaque morphology, can be highly dynamic over time, the effects of high PSS and/or PSS heterogeneity on plaque stability would be expected to occur closer to the time of high stress.

Similar to PSS, endothelial shear stress (ESS) has been shown recently to provide incremental risk stratification of untreated coronary lesions beyond IVUS plaque characterization (17). PSS describes the stress located inside an atherosclerotic plaque and is affected by vessel expansion and stretch by exposure to arterial pressure, whereas ESS describes the parallel friction force exerted by blood flow on the endothelial surface of the arterial wall. As PSS and ESS refer to different biomechanical forces, it is possible that the combination of ESS and PSS may improve plaque risk stratification further. Ultimately the combination of patient characteristics, plaque morphology, and biomechanical and inflammation plaque profiling may allow identification of those NCLs that will proceed to MACE, thus allowing more aggressive secondary prevention and also perhaps earlier definitive treatment.

STUDY LIMITATIONS. First, PSS calculations were applied retrospectively, and prospective studies should be performed to confirm the additive value of PSS and other PSS-related parameters in plaque risk assessment. However, propensity score matching ensured that a well-matched control group was used for comparison. Second, MACE in the PROSPECT study were largely driven by hospitalization for progressive and unstable angina, and although this could be due to plaque rupture with subsequent healing, other forms of plaque destabilization or plaque growth may be responsible. Third, PSS calculations based on VH-IVUS are limited by the resolution and ability of VH-IVUS to identify plaque components. However, IVUS is the only intravascular imaging modality to date with prospective clinical data. Finally, the role of ESS was not investigated, which can be important in a study where clinical events are likely driven by plaque growth. Combined PSS and ESS of the PROSPECT study would be of huge interest.

CONCLUSIONS

PSS and variations in PSS in the peri-MLA regions were increased in nonculprit plaques, leading to MACE in the PROSPECT study across a variety of plaque subtypes. Longitudinal heterogeneity in PSS was also increased in plaques leading to MACE, especially VH-TCFAs. Incorporation of PSS and heterogeneity in PSS improves the ability of IVUS to predict MACE, suggesting that biomechanical modeling may have a role in coronary atherosclerotic plaque risk stratification.

ADDRESS FOR CORRESPONDENCE: Prof. Martin R. Bennett, Division of Cardiovascular Medicine, University of Cambridge, Level 6, ACCI, Addenbrooke’s Hospital, Cambridge CB2 0QQ, United Kingdom. E-mail: mrb@mole.bio.cam.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: PSS, variations in PSS and longitudinal heterogeneity in PSS is increased in the peri-MLA regions of plaques, including VH-TCFA, which proceed to future MACE. Incorporation of such biomechanical analysis improves the ability of IVUS to identify high-risk plaques.

TRANSLATIONAL OUTLOOK: PSS, which may be estimated from VH-IVUS images, has been proposed as a mechanism that determines rupture in high-risk regions. This study provides further evidence that PSS and other associated features may better identify plaques that cause future patient events, allowing earlier and more aggressive treatment of relevant risk factors.
REFERENCES

1. World Health Organization. Cardiovascular diseases (CVDs). Fact Sheet. Reviewed May 2017. Geneva, Switzerland: WHO. Available at: https://www.who.int/cardiovascular_diseases/en/. Accessed July 2019.

2. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

3. Dohi T, Mintz GS, McPherson JA, et al. Non-fibroatheroma lesion phenotype and long-term clinical outcomes: a substudy analysis from the PROSPECT study. J Am Coll Cardiol Img 2013;6:908–16.

4. Calvert PA, Obaid DR, O’Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) study. J Am Coll Cardiol Img 2011;4:894–901.

5. Cheng JM, Garcia-Garcia HM, de Boer SP, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the AtheroRemodelIVUS study. Eur Heart J 2014;35:639–47.

6. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet 1989;2:941–4.

7. Tang D, Teng Z, Canton G, et al. Sites of rupture in human atherosclerotic carotid plaques are associated with high structural stresses: an in vivo MRI-based 3D fluid-structure interaction study. Stroke 2009;40:3258–63.

8. Teng Z, Brown AJ, Calvert PA, et al. Coronary plaque structural stress is associated with plaque composition and subtype and higher in acute coronary syndrome: the BEACON I (Biomechanical Evaluation of Atheromatous Coronary Arteries) study. Circ Cardiovasc Imaging 2014;7:461–70.

9. Costopoulos C, Huang Y, Brown AJ, et al. Plaque rupture in coronary atherosclerosis is associated with increased plaque structural stress. J Am Coll Cardiol Img 2017;10:1472–83.

10. Brown AJ, Teng Z, Calvert PA, et al. Plaque structural stress estimations improve prediction of future major adverse cardiovascular events after intracoronary imaging. Circ Cardiovasc Imaging 2016;9. pii: e004172.

11. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–75.

12. Chenou PK, Finn AV, Gardner C, et al. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. J Am Coll Cardiol 2007;50:940–9.

13. Fuji K, Masutani M, Okumura T, et al. Frequency and predictor of coronary thin-cap fibroatheroma in patients with acute myocardial infarction and stable angina pectoris a 3-vessel optical coherence tomography study. J Am Coll Cardiol 2008;52:787–8.

14. Fukumoto Y, Hiro T, Fuji T, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. J Am Coll Cardiol 2008;51:645–50.

15. Sabatine MS, Giugliano RP, Keech AC, et al., for the Committee FS Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

16. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.

17. Stone PH, Maehara A, Coskun AU, et al. Role of low endothelial shear stress and plaque characteristics in the prediction of nonculprit major adverse cardiac events: the PROSPECT study. J Am Coll Cardiol Img 2018;11:462–71.

KEY WORDS intravascular imaging, myocardial infarction, plaque structural stress, thin-cap fibroatheroma

APPENDIX For an expanded Methods as well supplemental tables and figures, please see the online version of this paper.
Stratifying the risks of individual coronary artery plaques to identify features associated with plaque progression and plaque destabilization and of major adverse cardiovascular events (MACE) has evolved substantially over the past few years as new relationships concerning plaque pathobiology and the influence of biomechanical forces have become evident. Lesion-based prognostication in early landmark studies (PROSPECT [Providing Regional Observations to Study Predictors of Events in the Coronary Tree] [1], VIVA [VH-IVUS in Vulnerable Atherosclerosis] [2], and AtheroRemoIVUS [European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis-Intravascular Ultrasound Study] trials [3]) was based on anatomic characterization of plaque alone (plaque burden [PB], thin cap fibroatheroma morphology, and minimal lumen area [MLA]), and a plaque was defined as $\geq 3$ consecutive virtual histology-intravascular ultrasound (VH-IVUS) frames (interslice distance of 0.4 mm) with PB $\geq 40\%$, such that a potential culprit lesion was centered around the MLA and could potentially be a short lesion. The per-plaque predictive accuracy for predicting a future MACE based on these baseline plaque characteristics was low, likely related to reliance on the anatomic characteristics alone, as well as perhaps the limited spatial region of the window of interest for consideration of destabilizing pathobiologic influences.

Recent evidence has convincingly shown, however, that plaques are often not a simple focal “mountain” or “volcano” centered around an MLA but a very complex and lengthy pathobiological lesion (a “mountain range”) with many different constituents, shapes, and resultant pathobiological and biomechanical forces along its heterogeneous longitudinal course. In the PREDICTION (Prediction of Progression of Coronary Artery using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics) study, for example, the mean plaque length in 371 plaques from 219 patients was 17 mm (most plaques ranged from 12 to 30 mm) [4], and as the individual plaque length increased, there were significantly increased numbers of distinct regions with different arterial remodeling patterns and different focal shear stress patterns within the same plaque. Plaque structural stress (PSS) was also observed to vary markedly along the course of a single plaque, especially in the setting of a large PB [5,6]. A recent near infrared spectroscopy-intravascular ultrasound (NIRS-IVUS) cross-sectional study of the spatial relationships among important plaque features further demonstrated that the locations of the maximum PB, minimum endothelial shear stress (ESS), maximum ESS, and maximum lipid core burden index (maxLCBI$_{4\text{mm}}$) were spatially discordant from the MLA in most arteries [7]. The site of maximum ESS was found most frequently at, or 3 mm upstream from, the site of MLA, whereas up- and downstream from the MLA was the location of the minimum ESS [7,8] and, in most plaques, the maximum PB [7]. These potentially destabilizing features were found up to 12 mm from the MLA in many longer plaques. A recent IVUS study demonstrated that plaque rupture occurred at the site of the MLA in only 16% of culprit lesions, whereas the site of...
plaque rupture was either substantially upstream or downstream from the MLA location in >80% of cases (9).

The current study by Costopoulos et al. in this issue of JACC (10) adds important insight concerning the longitudinal heterogeneity of plaque and the effect of that heterogeneity on the plaque’s proclivity to destabilize and cause a new MACE. From the PROSPECT study, the investigators evaluated 35 nonculprit plaques associated with subsequent MACE and compared them with 66 nonculprit plaques not associated with MACE (each with PB of ≥60% at the MLA). Although plaque composition by VH-IVUS was similar along the plaque length in both plaque groups (mean plaque length: 24 to 30 mm), there was marked heterogeneity of PSS along the entire plaque length, including over short distances. PSS and the heterogeneity in PSS were higher in MACE plaques along an 8-mm plaque length (4 mm upstream and downstream from the MLA) than in plaques not associated with future MACE, even though the PB was relatively constant. Including PSS along with plaque anatomic assessment markedly improved the identification of plaques associated with future MACE, and this incremental prognostication increased even further by incorporating a heterogeneity index of PSS (defined as the standard deviation of PSS divided by mean PSS or variation in PSS in the region of interest).

As Costopoulos et al. (10) appropriately speculate, prognostication incorporating PSS and ESS, as well as other anatomic, biomechanical, and inflammatory activity, may lead us closer to the ultimate goal of sufficiently accurate risk stratification of individual plaques to justify preemptive interventions to avert MACE outcomes. Local arterial remodeling behavior will likely also be very important to include, because that will impact local blood flow patterns in the microenvironment along the course of the plaque and the pathobiological consequences. The mechanistic reason why plaques, even ostensibly high-risk plaques, may stabilize may be that the arterial wall remodels in response to the presence of a plaque in its wall so that the plaque anatomic substrate may become quiescent as the pathobiological stimulus for plaque destabilization (low or high ESS) becomes more normalized to a physiologic level (4,11).

It will also be important to broaden our prognostic investigational focus on factors associated with plaque destabilization and MACE that are not associated with distinct plaque rupture, such as plaque erosion leading to acute coronary syndrome (12) or intra-plaque hemorrhage leading to abrupt conformation change and sudden worsening of stable angina (8,13). We are learning more concerning the plaque constituents and their contribution towards stabilization or destabilization and our prognostication is certainly improving as we broaden our field of view to incorporate the markedly heterogeneous and lengthy nature of plaques.

ADDRESS FOR CORRESPONDENCE: Dr. Peter H. Stone, Division of Cardiovascular Medicine, Brigham & Women’s Hospital, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115. E-mail: pstone@partners.org.

REFERENCES
1. Stone GW, Maehara A, Lansky AJ, et al., for the PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35.
2. Calvert PA, Obaid DR, O’Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIIVA (VHIVUS in Vulnerable Atherosclerosis) study. J Am Coll Cardiol Img 2011;4:894-901.
3. Cheng JM, García-García HM, de Boer SPM, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the AtheroRemoIVUS study. Eur Heart J 2014;35:639-47.
4. AntoniadiS AP, Papafaklis MI, Takahashi S, et al. Arterial remodeling and endothelial shear stress exhibit significant longitudinal heterogeneity along the length of coronary plaques. J Am Coll Cardiol Img 2016;9:1007-9.
5. Brown AJ, Teng Z, Calvert PA, et al. Plaque structural stress estimations improve prediction of future major adverse cardiovascular events after intracoronary imaging. Circ Cardiovasc Imaging 2016;9:e004172.
6. Dorada P, Otsuka K, Nadkarni A, et al. Biomechanical stress profiling of coronary atherosclerosis. Identifying a multifactorial metric to evaluate plaque rupture risk. J Am Coll Cardiol Img 2020;13:804-16.
7. Varshney AS, Coskun AU, Maynard CC, Croce KJ, Cormier MA, Cefalo NV, et al. Relationship between local endothelial shear stress and near-infrared spectroscopy lipid signal in patients with coronary artery disease: implications for plaque destabilization [Abstr]. Circulation 2018;138 Suppl 1:A11810.
8. Stone PH, Maehara A, Coskun AU, et al. Role of low endothelial shear stress and plaque characteristics in the prediction of nonculprit major adverse cardiac events: the PROSPECT study. J Am Coll Cardiol Img 2018;11:462-71.
9. Lee JM, Choi G, Hwang D, et al. Impact of longitudinal lesion geometry on location of plaque rupture and clinical presentations. J Am Coll Cardiol Img 2017;10:677-88.
10. Costopoulos C, Maehara A, Huang Y, et al. Heterogeneity of plaque structural stress is increased in plaques leading to MACE: insights from the PROSPECT study. J Am Coll Cardiol Img 2020;13:1026-18.
11. Koskinas KC, Chatzizisis YS, Coskun AU, et al. Natural history of experimental coronary atherosclerosis and vascular remodeling in relation to endothelial shear stress: a serial, in-vivo IVUS study. Circulation 2010;121:2092-101.
12. Franck G, Mawson T, Sausen G, et al. Flow perturbation mediates neutrophil recruitment and potentiates endothelial injury via TLR2 in Mice. Implications for superficial erosion. Circ Res 2017;121:31-42.
13. Michel J-B, Virmani R, Arbustini E, Pasterkamp G. Intraplaque haemorrhages as the trigger of plaque vulnerability. Eur Heart J 2011;32:1977-85.

KEY WORDS endothelial shear stress, intravascular imaging, myocardial infarction, plaque structural stress, thin-cap fibroatheroma
Myocardial fibrosis, either focal or diffuse, is a common feature of many cardiac diseases and is associated with a poor prognosis for major adverse cardiovascular events. Although histological analysis remains the gold standard for confirming the presence of myocardial fibrosis, endomyocardial biopsy is invasive, has sampling errors, and is not practical in the routine clinical setting. Cardiac imaging modalities offer noninvasive surrogate biomarkers not only for fibrosis but also for myocardial edema and infiltration to varying degrees, and have important roles in the diagnosis and management of cardiac diseases. This review summarizes important pathophysiological features in the development of commonly encountered cardiac diseases, and the principles, advantages, and disadvantages of various cardiac imaging modalities (echocardiography, single-photon emission computer tomography, positron emission tomography, multidetector computer tomography, and cardiac magnetic resonance) for myocardial tissue characterization, with an emphasis on imaging focal and diffuse myocardial fibrosis. (J Am Coll Cardiol Img 2020;13:1221–34) © 2020 by the American College of Cardiology Foundation.

Myocardial diseases are characterized by changes in tissue composition, such as the development of myocardial fibrosis, edema, or infiltration with fat, iron, or amyloid. Modifications in the extracellular matrix may lead to diastolic and/or systolic dysfunction, increasing the risk of adverse cardiovascular events (1,2). Therefore, the early detection of structural myocardial changes is of major diagnostic and prognostic value. The gold standard technique to assess histological alterations, especially myocardial fibrosis, is endomyocardial biopsy. However, sampling errors, the invasive nature of endomyocardial biopsy, and its inability to quantify the fibrotic burden of the entire myocardium have limited its use (3). Cardiac imaging modalities (echocardiography, single-photon emission computer tomography [SPECT], positron emission tomography [PET], multidetector computer tomography [MDCT], and cardiovascular magnetic resonance [CMR]) offer the ability to detect pathophysiological myocardial changes such as fibrosis, edema, and infiltration to varying degrees, and have important roles in the diagnosis, management, and prognostic assessment of cardiac diseases.

In this state-of-the-art review, we present the role of noninvasive imaging techniques in myocardial tissue characterization, with an emphasis on fibrosis imaging, in clinical applications.
**ABBREVIATIONS AND ACRONYMS**

- **18F-FDG**: 18-fluorodeoxyglucose
- **CMR**: cardiovascular magnetic resonance
- **ECV**: extracellular volume
- **GBCA**: gadolinium-based contrast agent
- **LGE**: late gadolinium enhancement
- **LV**: left ventricular
- **MDCT**: multidetector computed tomography
- **PET**: positron emission tomography
- **SPECT**: single-photon emission computed tomography
- **Tc-99m**: technetium-99m

**PATHOPHYSIOLOGY**

**MYOCARDIAL EDEMA.** Acute myocardial injury is followed by water dispersion in the intracellular and interstitial spaces, as a consequence of ischemic acidosis, vasodilation, and increased capillary permeability (4). Edema is an important component of acute myocardial processes of varied etiologies, including myocardial infarction, myocarditis, stress cardiomyopathy, and heart transplantation graft rejection, and is associated with left ventricular (LV) systolic and diastolic dysfunction (5).

**MYOCARDIAL FIBROSIS.** Fibrosis is a common pathological feature of many cardiac diseases that results in increased wall stiffness, cardiac remodeling, and heart failure (6). Importantly, myocardial fibrosis is a major prognostic factor of adverse cardiac events (7).

There are 2 main types of myocardial fibrosis. 1) Reactive interstitial fibrosis, which is characterized by a diffuse microscopic distribution in the myocardium and sometimes by localized perivasculature distribution, seen in arterial hypertension, valvular heart disease, diabetic cardiomyopathy, hypertrophic cardiomyopathy, idiopathic-dilated cardiomyopathy, and the aging heart. In contrast to replacement fibrosis, interstitial fibrosis is not induced by cell death and is a gradual process that can be reversed, if the cause is treated promptly (8). It is considered a marker of disease severity. If the condition worsens, it is followed by myocyte apoptosis and irreversible replacement fibrosis (6). 2) Replacement fibrosis typically occurs after myocyte injury or death, mostly in acute ischemic conditions, in which cell apoptosis triggers fibroblasts and promotes deposition of collagen fibrous tissue in the myocardium (9). It usually follows a localized macroscopic distribution. Replacement myocardial fibrosis may also occur in myocarditis, hypertrophic cardiomyopathy, idiopathic-dilated cardiomyopathy, sarcoidosis, and may demonstrate a diffuse distribution in toxic cardiomyopathies, chronic renal insufficiency, and as part of systemic inflammatory diseases (10). It is often present in the terminal stages of heart failure.

Another subtype of fibrosis is infiltrative interstitial fibrosis induced by the progressive deposition of insoluble amyloid (amyloidosis) or glycosphingolipids (Anderson-Fabry disease) in the heart (3).

**MYOCARDIAL FAT INfiltrATION.** Fat naturally develops around the heart, as peri-coronary adipose tissue or epicardial fat, mainly adjacent to the right ventricle. Abnormal myocardial fat infiltration has been described in arrhythmogenic cardiomyopathy, cardiac lipoma, tuberous sclerosis complex, and other cardiomyopathies. Lipomatous metaplasia also occurs in some chronic scars in ischemic cardiomyopathy (11).

**MYOCARDIAL IRON INFILTRATION.** Myocardial iron overload is characterized by the accumulation of excess body iron in the heart. Iron initially infiltrates the ventricular myocardium, and subsequently, the atrium, progressively leading to iron overload cardiomyopathy (12).

**MYOCARDIAL AMYLOID INFILTRATION.** The term “amyloid” is used to describe abnormal extracellular, insoluble, protein fibrils that resist proteolysis and infiltrate many organs (13). Cardiac amyloidosis is characterized by extracellular amyloid infiltration throughout the heart (13). Amyloid deposits impair myocardial contractile function and electrical conduction.

**IMAGING MODALITIES FOR MYOCARDIAL TISSUE CHARACTERIZATION**

**ECHOCARDIOGRAPHY.** Myocardial reflectivity to ultrasound and the analysis of backscatter signal have been used as a noninvasive method of tissue characterization and marker of collagen deposition (14). A greater calibrated integrated backscatter is indicative of greater fibrosis (Figure 1). Ultrasound elasticity imaging has been developed to measure the static stiffness of tissues. This technique can be thought of as palpating the tissues virtually using ultrasound (15). Although there is some correlation between calibrated integrated backscatter and fibrosis in patients with extensive myocardial fibrosis, this relationship is less clear in patients with milder degrees of fibrosis (16). Shear-wave elasticity imaging can also detect dynamic stiffness changes during the cardiac cycle (15). Overall, ultrasonic reflection techniques have not been widely used in clinical practice for quantification of fibrosis because they lack sensitivity, and therefore, have been surpassed by novel CMR techniques.

Tissue Doppler imaging and speckle tracking echocardiography can measure myocardial strain. Regional strain is a dimensionless measurement of myocardial deformation, expressed as a fractional or proportion change from an object’s original dimension. Strain rate refers to the speed at which myocardial deformation (i.e., strain) occurs. These parameters correlate inversely with systolic and diastolic dysfunction and may reveal functional abnormalities in fibrotic processes earlier than conventional echocardiographic techniques (17-19).
Overall, compared with late gadolinium enhancement (LGE) CMR, strain imaging using echo has moderate diagnostic capacity to detect fibrosis, because it focuses on functional measures, rather than tissue characteristics, as a surrogate marker of fibrosis.

Nonspecific surrogate echocardiographic markers, such as regional increase in LV thickness and mass, have been used to suggest the presence of myocardial edema. High-frequency ultrasound techniques have been reported to indirectly characterize myocardial water content by quantification of alterations in mechanical properties of tissue (18).

Echocardiographic characteristics such as “sparking” myocardial texture, hypertrophy of the ventricles, thickening of heart valves, and a restrictive LV filling pattern suggest the diagnosis of cardiac amyloidosis. In this condition, LV global longitudinal strain is significantly reduced at the basal and mid segments of the LV (Figure 2), whereas the deformation of the apical segments may be preserved (apical sparing). In Anderson-Fabry disease, patients with myocardial fibrosis of the basal posterolateral LV wall on CMR show more impaired LV global longitudinal strain compared with patients without myocardial fibrosis, despite having preserved LV ejection fraction. Furthermore, patients with proven cardiac sarcoidosis on CMR have significantly more impaired global longitudinal strain compared with control subjects.

**NUCLEAR IMAGING**

**SPECT.** SPECT myocardial perfusion imaging is well-established for the evaluation of patients with known or suspected coronary artery disease. Irreversible perfusion defects are indirect markers of fibrosis (19), whereas molecular imaging is more specific for collagen formation. Avß3 integrin is expressed by activated cardiac myofibroblasts and endothelial cells and represents a target for angiogenesis and scar formation post–myocardial infarction. Cy5.5-RGD imaging peptide labeled with technetium-99m (Tc-99m) binds to such targets to evaluate myocardial remodeling (20). Increased uptake of radiolabeled angiotensin II receptor blocker (Tc-99m losartan) demonstrated histologically proven proliferative activity of myofibroblasts 12 weeks post–myocardial infarction (21).
This multidisciplinary work-up of a patient with cardiac transthyretin amyloidosis with an Se77Tyr variant displayed (A) a strain pattern characteristic of an infiltrative process, (B) a 4-chamber cine steady-state free precession image and corresponding late gadolinium enhancement (LGE) image showing transmural LGE, and (C) whole-body anterior technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy and hybrid single-photon emission computed tomography–computed tomography showing Perugini grade 1 abnormal uptake. Reprinted with permission from Martinez-Naharro et al. (86).
Bone scintigraphy (Figure 2) using Tc-99m-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid, Tc-99m-labeled pyrophosphate, and Tc-99m-labeled hydroxymethylene diphosphonate is highly sensitive for imaging cardiac transthyretin amyloidosis. When scintigraphy is combined with biochemical testing for a monoclonal protein in serum and urine, cardiac transthyretin amyloidosis can be diagnosed in the absence of histology with >98% certainty.

PET. The perfusable tissue index has been used as an indirect marker of myocardial fibrosis. A reduction of this index has been shown to correlate with the extent of fibrosis estimated with CMR in ischemic heart disease. Furthermore, the index has been shown to be reduced in patients with advanced dilated cardiomyopathy, indicating possible interstitial fibrosis.

Markedly reduced or absent 18-fluorodeoxyglucose (18F-FDG) uptake indicates fibrosis, and FDG-PET is mainly used to assess myocardial viability. Molecular PET may assess mechanisms underlying fibrosis formation, but current techniques remain at an experimental stage and need to be validated in clinical studies.

Cardiac PET may be useful to detect cardiac sarcoidosis and monitor response to therapy (26). Cardiac 18F-FDG PET studies for sarcoidosis should combine both perfusion imaging and 18F-FDG imaging (Figure 3) to differentiate the patterns of disease (27). A high-fat, low-carbohydrate diet followed by prolonged fasting is needed to suppress physiological myocardial glucose uptake.

MDCT. Myocardial infarction is depicted as a low density, unenhanced area in arterial phase MDCT and as a hyperenhanced area in late-phase MDCT. Fibrosis identification with MDCT has shown satisfactory agreement with LGE CMR, particularly in ischemic heart disease (28). A key feature of acute infarction is myocardial edema, which presents with CT values near zero due to increased water content. Evidence from experimental models of acute infarction showed substantial correlation between unenhanced dual-source CT and T2-weighted CMR to detect myocardial edema (29). The area presenting with edema in unenhanced CT, but without delayed enhancement in the late phase, is likely to correspond to the salvageable area at risk.

The use of MDCT to detect diffuse abnormalities of myocardial tissue is significantly more challenging than the evaluation of regional scar, due to the low contrast resolution. A small study in patients with heart failure and healthy individuals found a good...
correlation ($r = 0.82; p < 0.001$) between CMR and MDCT-derived extracellular volume (ECV) (30), but only the anterior and anterolateral myocardial segments could be reliably analyzed. Another small study in patients with aortic stenosis demonstrated that ECV, measured using an equilibrium CT technique, correlated well with histological quantification of myocardial fibrosis and ECV measured using equilibrium CMR (31). MDCT was also used to detect intramyocardial fibrosis in patients with hypertrophic cardiomyopathy (32) and myocardial iron overload (33).

**CMR.** CMR is not only accurate in the assessment of cardiac anatomy and function but is also superior in noninvasive myocardial tissue characterization, outweighing other imaging modalities in its multiparametric capabilities for a comprehensive cardiac examination (Central Illustration). T1- and T2-weighted sequences are a basic way to perform tissue characterization. T1 relaxation time is shortened by gadolinium-based contrast agents (GBCAs), and LGE images may be used to highlight areas of focal fibrosis compared with normal myocardium. Myocardial fibrosis causes significant expansion of the extracellular space, leading to a higher regional concentration of GBCAs and an area of relative hyperenhanced signal (34). Mapping techniques allow direct, pixel-by-pixel quantitative myocardial tissue characterization without the need for presumed normal reference regions of interest to highlight areas of disease. The principles of mapping techniques are reviewed elsewhere (35). Briefly, native (pre-contrast) T1 mapping reflects a composite signal from both the intracellular (mainly myocytes) and extracellular myocardial compartments. Each tissue type exhibits a characteristic range of normal T1 relaxation times at a particular field strength, deviation from which may be indicative of disease or a change in physiology. T1 relaxation times are prolonged by increased free water content in tissues, and are generally shortened by iron, fat, and GBCAs. Areas of fibrosis and ECV expansion are characterized by accumulation of water, which typically prolongs native T1 time. The myocardial ECV can be quantified using pre- and post-contrast myocardial and blood T1 values, adjusting for the blood hematocrit. Pixel-wise ECV maps can also be created. Myocardial ECV may act as a surrogate marker of fibrosis when other pathologies that increase the extracellular space, such as myocardial edema and/or inflammation, infiltration (2), and ischemia (36), have been excluded. T2 mapping quantifies T2 myocardial relaxation times and is mainly used to detect edematous myocardium.
**Acute myocardial infarction.** Acute ischemic injury leads to downstream myocardial edema and eventual infarction, sometimes with complications—such as microvascular obstruction and intramyocardial hemorrhage—all which can be visualized using CMR. Infarct size can be assessed on LGE imaging, although this may be overestimated in the acute setting due to expansion of the extracellular space by edema. Conventionally, the area at risk is delineated using T2-weighted edema imaging. Newer mapping techniques, such as T1 and T2 mapping, correlate well with the area at risk measured by microspheres in animal studies (37) and may be more sensitive for directly quantifying the area at risk (35). Microvascular obstruction may be seen on resting first-pass perfusion, early gadolinium enhancement, or LGE images, with good correlation to histopathology, and confers a poor prognosis (38). Intramyocardial hemorrhage associated with reperfusion injury is seen as signal voids on T2-weighted images or shortened T2, T2*, or T1 relaxation times on mapping techniques (39) caused by the breakdown products of hemoglobin and oxidized iron, which are paramagnetic (Figure 4). Mapping techniques have shown their usefulness in characterizing acute myocardial infarction, demonstrating increased T1, T2, and ECV in the area at risk, the infarct zone, and even remote myocardium, offering additional insights into acutely infarcted myocardium (35). CMR imaging markers not only offer validated surrogates of pathophysiology in the assessment of acute myocardial infarction, but also confer prognosis that may be useful for risk stratification of the individual patient (40).

**Acute myocardial inflammation and edema.** Inflammation results in edema and is a common feature of both acute ischemic and nonischemic myocardial injury. The pathophysiological changes in acute myocarditis, including edema, hyperemia and/or capillary leak, and myocyte necrosis, may be visualized on T2-weighted, early gadolinium enhancement, and LGE imaging, respectively. The newer mapping techniques, including T1 mapping, T2 mapping, and ECV, circumvent many of the known technical limitations of conventional CMR techniques in the detection of myocarditis, with promising initial results that point to their likely superiority (Figure 5) (36,41-47). A recent meta-analysis in patients with acute myocarditis showed that native T1 mapping had superior diagnostic accuracy across all CMR tissue characterization methods (44). In contrast, because T1 mapping and ECV might detect both acute and chronic changes, some reports suggest that T2 mapping might be more specific to acute myocardial edema and inflammation (48,49).

**Myocardial fibrosis detection using LGE.** LGE is still considered the clinical gold standard for identifying
areas of myocardial infarction with high spatial resolution, including small subendocardial scars that may be missed by SPECT (50). Multiple studies have demonstrated excellent spatial correlation between areas of myocardial scarring identified on LGE imaging and histopathology, both in the acute and chronic phases of infarction (51). The transmural extent of infarction on LGE inversely predicts the likelihood of regional contractile recovery after revascularization (52) and is the current CMR standard for myocardial viability assessment.

LGE in a predominantly nonischemic (non-subendocardial) pattern is also present in a significant proportion of patients with nonischemic myocardial injury and cardiomyopathies (10). Its presence is strongly associated with poor prognosis, including increased risk of all-cause mortality, heart failure hospitalization, and sudden cardiac death (53). Depending on the LGE pattern and distribution, CMR may, together with functional and morphological imaging, be used to diagnose specific cardiomyopathies (detailed review elsewhere [10]). Areas with LGE in nonischemic cardiomyopathies often correlate to (although are not specific for) areas of focal fibrosis on histopathology. For instance, the areas of mid-wall and subepicardial LGE typically seen in myocarditis (Figure 5) correlate to areas of inflammation, myocyte necrosis, and fibrosis (54). In dilated cardiomyopathy, mid-wall enhancement often seen in the interventricular septum (and

(A) Dark-blood T2-weighted imaging showed global and focal increased myocardial T2 signal intensity, with a T2 signal intensity ratio compared with skeletal muscle (not shown) of >3.0, consistent with severe acute edema. (B) T2 mapping showed global increase in myocardial T2 values of 89 ± 7 ms, consistent with edema. (C) LGE imaging showed multiple areas of mid-wall, subepicardial, and patchy enhancement in a noncoronary distribution. (D) Native T1 mapping using the SHMOLLI (Shortened MOdified Look-Locker Inversion recovery) method showed significantly increased global myocardial T1 values (1,048 ± 79 ms; normal 962 ± 25 ms), and up to 1,240 ms in focal areas of injury. (E) Post-gadolinium contrast T1 mapping (at 15 min) showed areas of low T1 in areas of LGE. (F) Extracellular volume (ECV) mapping showed significantly expanded ECV of 43% (normal 27 ± 3%). Reprinted with permission from Ferreira VM, J de Lara Fernandes, C Basso, Friedrich MG. Myocarditis: Lombardi M, Ferrari V, Bucciarelli-Ducci C, Petersen S, Plein S, editors. The EACVI Textbook of Cardiovascular Magnetic Resonance. Oxford, United Kingdom: Oxford University Press. Abbreviations as in Figures 2 and 4.
sometimes in the inferolateral walls) corresponds to areas of macroscopic fibrosis and microscopic collagen deposition admixed with myocytes on histopathology. The patient with no LGE had normal native T1 and ECV maps; the patient with subendocardial LGE had borderline T1 values and high ECV values, and in the patient with transmural LGE, very high native T1 values and very high ECV values were seen. Reprinted with permission from Martinez-Naharro et al. (86). Abbreviations as in Figure 4 and 5.

**STUDY LIMITATIONS OF LGE IN DETECTING DIFFUSE FIBROSIS.** LGE imaging, although powerful in detecting areas of focal fibrosis, has limitations for detecting diffuse myocardial fibrosis. It requires regions of presumed normal myocardium to provide the necessary contrast between affected and unaffected tissue, which may not be available in diffuse pathology. The development of T1 mapping has enabled the identification and quantification of not only focal, but also diffuse myocardial fibrosis.
T1 MAPPING AND ECV QUANTIFICATION IN FOCAL FIBROSIS. In general, focal replacement fibrosis in chronic myocardial infarction, as identified by LGE, exhibits high native T1 and ECV values (62–64). Native T1 mapping may provide a contrast-free method for myocardial infarction detection, especially in patients with severely impaired renal function who had GBCAs are contraindicated (65). However, lipomatous metaplasia may occur in some chronic myocardial scars, leading to lowered pseudo-normalized or even paradoxically elevated T1 values due to fat bias (35). Furthermore, apparently unaffected remote myocardium on LGE imaging in acute and chronic myocardial infarction exhibits abnormal T1 and ECV values (63,66) and may identify myocardium prone to adverse cardiac remodeling, worsening of contractile function, and poorer prognosis (66). In nonischemic heart disease, such as myocarditis, sarcoidosis, dilated cardiomyopathy, and hypertrophic cardiomyopathy, areas of focal fibrosis seen on LGE generally demonstrate high T1 and ECV values (2).

T1 MAPPING AND ECV QUANTIFICATION IN DIFFUSE MYOCARDIAL FIBROSIS. The measurement of T1 and ECV has known dependencies on age and sex (67). As discussed earlier, elevated T1 or ECV values may not necessarily reflect the development of diffuse myocardial fibrosis, must be interpreted within the clinical context after exclusion of confounders, and typically include the use of age- and sex-matched controls. Native T1 and ECV quantification generally show good correlation to collagen volume fraction and diffuse myocardial fibrosis on histopathology in animal models of hypertension (68) and clinical cohorts of heart failure, valvular heart disease, and heart transplantation patients with ischemic and nonischemic cardiomyopathies (69–72).

In dilated and hypertrophic cardiomyopathy, both T1 and ECV can detect abnormalities in apparently normal myocardium on LGE-CMR. Studies have shown that, in patients with dilated or hypertrophic cardiomyopathy, even segments with normal wall thickness and no LGE show increased T1 values (73), potentially due to the presence of diffuse myocardial fibrosis and/or other causes of increased free water content not readily detected by LGE. Patients with hypertrophic cardiomyopathy, including asymptomatic relatives who are genotype-positive but without LV hypertrophy, also demonstrate elevated ECV (74). In patients with dilated cardiomyopathy, elevated T1 values predict a higher risk for cardiovascular events and heart failure, and there is a strong correlation between elevated ECV and collagen volume fraction within the spectrum of patients with dilated cardiomyopathy (75). Patients with heart failure with preserved ejection fraction were shown to have elevated ECV compared with normal control subjects (76). Both T1 and ECV appear to have added value in detecting abnormalities and predicting prognosis in patients with heart failure and cardiomyopathies (77–80). The ability to detect diffuse myocardial fibrosis early may identify novel therapeutic targets and opportunities for early intervention before irreversible myocardial pathology and dysfunction develops.

Aortic stenosis is a condition characterized by a number of pathophysiological changes in the heart as the disease progresses, including LV hypertrophy,
resting coronary vasodilatation, and the development of diffuse and focal fibrosis. T1 and ECV have generally been observed to be elevated in moderate to severe aortic stenosis, and correlate to histological interstitial fibrosis and the collagen volume fraction (81). The expansion of the intravascular compartment, such as that seen in coronary vasodilatation, also contributes to elevation of T1, and thus, ECV. The stress/rest T1 response has been shown to normalize after aortic valve replacement in some patients with aortic stenosis (81). Thus, elevation of T1 and ECV in aortic stenosis is multifactorial. Myocardial ECV has been shown to be a stronger predictor of adverse cardiovascular outcomes than the extent of LV hypertrophy in aortic stenosis, demonstrating prognostic value (35). In the future, T1 and ECV may even play a role in the optimal timing of valve replacement in aortic stenosis. Systemic arterial hypertension is another condition that subjects the LV to an increased afterload, potentially leading to hypertrophy, and diastolic and systolic dysfunction. Native T1 and ECV are mildly elevated in patients with hypertension and LV hypertrophy compared with those without, which may reflect diffuse myocardial fibrosis (82). The degree of T1 or ECV elevation may help differentiate hypertensive heart disease from other LV hypertrophy phenotypes, such as hypertrophic cardiomyopathy, cardiac amyloidosis, or athlete’s heart.

**T1 AND/OR ECV IN ATHLETE’S HEART.** Recent studies that used CMR that showed normal or decreased ECV in athlete’s hearts support the notion that physiological LV hypertrophy was due to myocyte enlargement rather than an increased extracellular matrix (83). These studies were in contrast to findings of hypertrophic cardiomyopathy, in which pathological LV hypertrophy was shown to correlate directly with ECV. This suggested that a significant proportion of the LV mass was due to an increase in the extracellular matrix and that mapping might potentially be useful in differentiating athlete’s hearts from other forms of cardiomyopathy (83). Focal areas of fibrosis were demonstrated in up to 13% of elite and veteran athletes, both in histopathology and on CMR LGE, with an apparent dose–response of focal fibrosis to exercise (84). It was less clear whether high-intensity exercise first induced diffuse myocardial fibrosis that progressed to focal fibrosis, or whether there was a dose–response threshold of developing either focal or diffuse fibrosis in response to exercise in this setting (85). Longitudinal characterization of the cardiac phenotype in athletes would provide further insights.

**CMR for myocardial infiltration.** CMR has a major role in the diagnosis and prognostication of infiltrative myocardial pathology. Amyloid light-chain and cardiac transthyrein amyloidosis can be detected by a circumferential pattern of LGE in combination with a dark blood pool, which initially affects the subendocardium but expands transmurally as disease progresses (Figure 2) (86). T1 mapping techniques have high diagnostic accuracy for detecting cardiac amyloidosis (Figure 6) and probably greater sensitivity for detecting early disease compared with LGE-CMR (86,87). The degree of ECV expansion in established cardiac amyloidosis is beyond that of any other myocardial disease, making it almost pathognomonic, especially when combined with structural, functional, and clinical features. Myocardial native T1-mapping and ECV predict mortality in patients with systemic amyloidosis (80).

Myocardial fat can be easily detected with T1- or T2-weighted CMR as areas of bright signal. Native T1 mapping is also a good way to identify fat, with low T1 values in general, with the caveat of paradoxically high T1 values in voxels partially occupied by fat (88).

Anderson-Fabry disease, which is characterized by accumulation of intramyocardial sphingolipids, has a characteristic CMR phenotype. LV hypertrophy is accompanied by small areas of a diffuse LGE pattern (corresponding to areas with abnormal lipid accumulation), with a broad band of mid-wall enhancement localized to the basal inferolateral wall (corresponding to regions of dense collagen on histopathology) (89) (Figure 7). Native T1 mapping can distinguish these 2 populations of abnormal myocardial pixels, offering incremental value to LGE (89,90), and may also detect right ventricular involvement (91). T1 mapping may identify the Anderson-Fabry phenotype early as LV hypertrophy with low T1 values, differentiating it from other diseases with hypertrophy (89).

Myocardial iron overload has been shown to shorten T1, T2, and T2* values. The standard CMR technique for the detection of cardiac iron accumulation is T2* mapping, validated in animal and human studies (92), whereas T1 and T2 mapping show excellent quantitative agreement, with both showing good correlation to T2* (35,93).

**Conclusions**

Cardiac diseases often result in common pathophysiological processes, including myocardial edema, and the development of diffuse and focal fibrosis that portend a poor prognosis. In this regard, noninvasive imaging modalities provide important information
Cardiovascular Magnetic Resonance

HIGHLIGHTS

- Tissue composition changes such as fibrosis, edema, or infiltration are frequent features in myocardial diseases.
- Cardiac imaging modalities offer the ability to characterize myocardial tissue to varying extent.
- Cardiovascular magnetic resonance offers comprehensive myocardial tissue characterization by providing various diagnostic and prognostic imaging biomarkers.
- Advanced cardiac imaging is expected to become an integral part in risk stratification and personalized medicine.

REFERENCES

1. Bello D, Shah DJ, Farah GM, et al. Gadolinium cardiovascular magnetic resonance predicts reversible myocardial dysfunction and remodeling in patients with heart failure undergoing beta-blocker therapy. Circulation 2003;108:1945-53.
2. Ferreira VM, Piekny ski SK, Robson MD, Neubauer S, Karamitsos TD. Myocardial tissue characterization by magnetic resonance imaging: novel applications of T1 and T2 mapping. J Thorac Imaging 2014;29:147-54.
3. Mewton N, Liu CY, Croisille P, Blumenke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57:891-903.
4. Garcia-Dorado D, Andres-Villareal M, Ruiz-Meana M, Insero J, Barba I. Myocardial edema: a translational view. J Mol Cell Cardiol 2012;52:933-9.
5. Dongaonkar RM, Stewart RH, Geissler HJ, Laine GA. Myocardial microvascular permeability, interstitial oedema, and compromised cardiac function. Cardiovasc Res 2010;87:331
6. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991;83:1849-65.
7. Amable-Venkatesh B, Lima JA. Cardiac MRI: a central prognostic tool in myocardial fibrosis. Nat Rev Cardiol 2015;12:18-29.
8. Lopez B, Querejeta R, Gonzalez A, Sanchez E, Larman M, Diez J. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. J Am Coll Cardiol 2004;43:2028-35.
9. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000;101:2981-8.
10. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. J Am Coll Cardiol 2009;54:1407-24.
11. Arnold JR, Karamitsos TD, Pegg TJ, Francis JM, Neubauer S. Left ventricular lipomatous meta-plasia following myocardial infarction. Int J Cardiol 2009;137:e11-2.
12. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. Circulation 2011;124:2253-63.
13. Rambaram RN, Serpell LC. Amyloid fibrils: abnormal protein assembly. Prion 2008;2:112-7.
14. Picano E, Pelosi G, Marzilli M, et al. In vivo quantitative ultrasonic evaluation of myocardial fibrosis in humans. Circulation 1990;81:58-64.
15. Vejdani-Jahromi M, Freedman J, Kim YJ, Trahey GE, Wolf PD. Assessment of diastolic function using ultrasound elastography. Ultrasound Med Biol 2018;44:551-61.
16. Prior DL, Somaratne JB, Jenkins AJ, et al. Calibrated integrated backscatter and myocardial fibrosis in patients undergoing cardiac surgery. Open Heart 2015;2:e000278.
17. Jellis C, Martin J, Narula J, Marwick TH. Assessment of nonischemic myocardial fibrosis. J Am Coll Cardiol 2010;56:89-97.
18. dent CL, Scott MJ, Wickline SA, Hall CS. High-frequency ultrasound for quantitative characterization of myocardial edema. Ultrasound Med Biol 2000;26:375-84.
19. Beller GA, Heede RC. SPECT imaging for detecting coronary artery disease and determining prognosis by noninvasive assessment of myocardial perfusion and myocardial viability. J Cardiovasc Transl Res 2011;4:416-24.
20. Verjans JW, Lovhaug D, Narula N, et al. Noninvasive imaging of angiotsin receptors after myocardial infarction. J Am Coll Cardiol Img 2008;1:354-62.
21. van den Borne SW, Isobe S, Verjans JW, et al. Molecular imaging of interstitial alterations in remodeling myocardium after myocardial infarction. J Am Coll Cardiol 2008;52:2017-28.
22. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404-12.
23. Knaep P, Bondarenko O, Beek AM, et al. Impact of scar on water-perfusable tissue index in chronic ischemic heart disease: evaluation with PET and contrast-enhanced MRI. Mol Imaging Biol 2006;8:245-51.
24. Knaep P, Gotte MJ, Paulus WJ, et al. Does myocardial fibrosis hinder contractile function and perfusion in isomorphic dilated cardiomyopathy? PET and MR imaging study. Radiology 2006;240:380-8.
25. Saraste A, Knuuti J. PET imaging in heart failure: the role of new tracers. Heart Fail Rev 2017;22:501-11.
26. Chareonthaitawee P, Beanlands RS, Chen W, et al. Joint SNMMI-ASNC expert consensus document on the role of O18-FDG PET/CT in cardiac sarcoid detection and therapy monitoring. J Nucl Cardiol 2017;24:1741-58.
27. Aggarwal NR, Snijders Y, Young PM, Gersh BJ, Cooper LT, Chareonthaitawee P. Advances in imaging for diagnosis and management of cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging 2015;16:949-58.
28. Takada H, Funabashi N, Uehara M, Iida Y, Kobayashi Y. Diagnostic accuracy of CT for the detection of left ventricular myocardial fibrosis in various myocardial diseases. Int J Cardiol 2017;228:375-9.
29. Mahnken AH, Bruners P, Bornkoel CM, Kramer N, Guenther RW. Assessment of myocardial edema by computed tomography in...
myocardial infarction. J Am Coll Cardiol Img 2009; 2:1167-74.

30. Naef MS, Kavel N, Lee JJ, et al. Interstitial myocardial fibrosis assessed as extracellular volume fraction with low-radiation-dose cardiac CT. Radiology 2012;264:876-83.

31. Bandula S, White SK, Fielt AS, et al. Measurement of myocardial extracellular volume fraction by using equilibrium contrast-enhanced CT: validation against histologic findings. Radiology 2013; 269:396-403.

32. Langer C, Lutz M, Eden M, et al. Hypertrophic cardiomyopathy in cardiac CT: a validation study on the detection of intramyocardial fibrosis in consecutive patients. J Cardiovasc Imaging 2014;30:659-67.

33. Ibrahim el SH, Bowman AW. Characterization of myocardial iron overload by dual-energy computed tomography compared to T2 * MRI. A phantom study. Proceedings of Annual International Conference of the IEEE Engineering in Medicine and Biology Society 2014;2014:5133-6.

34. Karamitsos TD, Dall’Armellina E, Choudhury RP, Neubauer S. Ischemic heart disease: comprehensive evaluation by cardiovascular magnetic resonance. Am Heart J 2011;162:16-30.

35. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19:75.

36. Ntusi NBA, Francis JM, Matthews PM, Worthword PB, Neubauer S, Karamitsos TD. Myocardial and vascular dysfunction in patients with rheumatoid arthritis assessed with cardiovascular magnetic resonance: evidence of increased vascular risk. Heart 2013;99:A62-3.

37. Ugander M, Bagi PS, Oki AJ, et al. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. J Am Coll Cardiol Img 2012; 5:596-603.

38. Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. J Am Coll Cardiol Img 2014;7:940-52.

39. Bulluck H, Rosmini S, Abdel-Gadir A, et al. Residual myocardial iron following intramyocardial hemorrhage during the convalescent phase of refurposed ST-segment-elevation myocardial infarction and adverse left ventricular remodeling. Circ Cardiovasc Imaging 2016;9.

40. Khan JN, McCann GP. Cardiovascular magnetic resonance imaging assessment of outcomes in acute myocardial infarction. World J Cardiol 2017: 9:109-33.

41. Ferreira VM, Picchini SK, Dall’Armellina E, et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012; 14:42.

42. Bohmen S, Raduski UK, Lund GK, et al. Performance of T1 and T2 mapping cardiovascular magnetic resonance to detect active myocarditis in patients with recent-onset heart failure. Circ Cardiovasc Imaging 2015;8.

43. Ferreira VM, Picchini SK, Dall’Armellina E, et al. Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. J Cardiovasc Magn Reson 2014;16:36.

44. Kotanidis CP, Bazmani MA, Haidich AB, Karvounis C, Antoniades C, Karamitsos TD. Diagnostic accuracy of cardiovascular magnetic resonance in acute myocarditis: a systematic review and meta-analysis. J Am Coll Cardiol Img 2016;9:1583-90.

45. Ntusi N, D’Oywer E, Dorrell L, et al. HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. Circ Cardiovasc Imaging 2016;9:e004430.

46. Ferreira VM, Marcelino M, Picchini SK, et al. Pheochromocytoma is characterized by catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction. J Am Coll Cardiol 2016;67:2364-74.

47. Tahir E, Sinn M, Bohmen S, et al. Acute versus chronic myocardial infarction: diagnostic accuracy of quantitative native T1 and T2 mapping versus assessment of edema on standard T2-weighted cardiovascular MR images for differentiation. Radiology 2017;285:83-91.

48. von Knobelsdorff-Brenkenhoff F, Schuler J, Everett RJ, Stirrat CG, Semple SI, Newby DE, Stueck MR, Mirsadraee S. Assessment of myocardial fibrosis with T1 mapping MRI. Clin Radiol 2016;71:768-78.

49. Messroghli DR, Walters K, Plein S, et al. Myocardial T1 mapping: application to patients with acute and chronic myocardial infarction. Magn Reson Med 2007;58:34-40.

50. Liu A, Wijesurendra RS, Francis JM, et al. Adenosine stress and rest T1 mapping can differentiate between ischemic, infarcted, remote, and normal myocardium without the need for gadolinium contrast agents. J Am Coll Cardiol Img 2016;9:27-36.

51. Dall’Armellina E, Ferreira VM, Kharbanda RK, et al. Diagnostic value of pre-contrast T1 mapping in acute and chronic myocardial infarction. J Cardiovasc Magn Reson 2017;19:42.

52. Karamitsos TD, Dall’Armellina E, Armellina E, Ferreira VM, Kharbanda RK, et al. Quantification of cardiomyocyte hypertrophy by cardiac magnetic resonance: implications for early cardiac remodeling. Circulation 2013;128:1225-33.
69. Bull S, White SK, Piechnik SK, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart 2013;99:932–7.
70. de Meester de Ravenstein C, Bouzin C, Lazam S, et al. Histological validation of measurement of diffuse interstitial myocardial fibrosis by myocardial extracellular volume fraction from Modified Look-Locker imaging (MOLLI) T1 mapping at 3 T. J Cardiovasc Magn Reson 2015;17:48.
71. Kammenderlander AA, Marzulf BA, Zotter-Tufaro C, et al. T1 Mapping by CMR imaging: from histological validation to clinical implication. J Am Coll Cardiol Img 2016;9:14–23.
72. Ide S, Riesenkampf E, Chiasson DA, et al. Histological validation of cardiovascular magnetic resonance T1 mapping markers of myocardial fibrosis in pediatriic heart transplant recipients. J Cardiovasc Magn Reson 2017;19:50.
73. Dass S, Suttie JJ, Piechnik SK, et al. Myocardial tissue characterization using magnetic resonance non-contrast T1 mapping in hypertrophic and dilated cardiomyopathy. Circ Cardiovasc Imaging 2012;5:726–33.
74. Ho CY, Abbasi SA, Neelan TG, et al. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. Circ Cardiovasc Imaging 2013;6:415–22.
75. aus dem Siepen F, Buss SJ, Messroghli D, et al. T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. Eur Heart J Cardiovasc Imaging 2015;16:210–6.
76. Su MY, Lin LY, Tseng YH, et al. CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFrEF. J Am Coll Cardiol Img 2014;7:991–7.
77. Schelbert EB, Pieher KM, Zareba KM, et al. Myocardial fibrosis quantified by extracellular volume is associated with subsequent hospitalization for heart failure, death, or both across the spectrum of ejection fraction and heart failure stage. J Am Heart Assoc 2015;4(12).
78. Wong TC, Piehier K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. Circulation 2012;126:1206–16.
79. Puntmann VO, Carr-White G, Jabbour A, et al. T1-mapping and outcome in non-ischemic cardiomyopathy: all-cause mortality and heart failure. J Am Coll Cardiol Img 2016;9:40–50.
80. Banyersad SM, Fontana M, Maestrelli V, et al. T1 mapping and survival in systemic light-chain amyloidosis. Eur Heart J 2015;36:244–51.
81. Mahmud M, Piechnik SK, Levetl E, et al. Adenosine stress native T1 mapping in severe aortic stenosis: evidence for a role of the intravascular compartment on myocardial T1 values. J Cardiovasc Magn Reson 2014;16:92.
82. Treibel TA, Zemnak F, Sado DM, et al. Extracelular volume quantification in isolated hyper tension – changes at the detectable limits? J Cardiovasc Magn Reson 2015;17:74.
83. Swooboda PP, McDermid AK, Erhayiem B, et al. Assessing myocardial extracellular volume by T1 mapping to distinguish hypertrophic cardiomyopathy from athlete’s heart. J Am Coll Cardiol 2016;67:2189–90.
84. Gati S, Sharma S, Pennell D. The role of cardiovascular magnetic resonance imaging in the assessment of highly trained athletes. J Am Coll Cardiol Img 2018;11:247–59.
85. Graham-Brown MP, McCann GP. T1 mapping in athletes: a novel tool to differentiate physiological adaptation from pathology? Circ Cardiovasc Imaging 2016;9:e004706.
86. Martinez-Naharro A, Treibel TA, AbdelGadir A, et al. Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol 2017;70:466–77.
87. Karamitsos TD, Piechnik SK, Banyersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol Img 2013;6:488–97.
88. Ferreira VM, Holloway CJ, Piechnik SK, Karamitsos TD, Neubauer S. Is it really fat? Ask a T1-map. Eur Heart J Cardiovasc Imaging 2013;14:1060.
89. Sado DM, White SK, Piechnik SK, et al. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging 2013;6:392–8.
90. Thompson RB, Chow K, Khan A, et al. Ti(t) mapping with cardiovascular MRI is highly sensitive for Fabry disease independent of hypertrophy and sex. Circ Cardiovasc Imaging 2013;6:637–45.
91. Pagano JJ, Chow K, Khan A, et al. Reduced right ventricular native myocardial T1 in Anderson-Fabry disease: comparison to pulmonary hypertension and healthy controls. PloS One 2016;11:e0157563.
92. Anderson LJ. Assessment of iron overload with T2* magnetic resonance imaging. Prog Cardiovasc Dis 2011;54:287–94.
93. Krittayaphong R, Zhang S, Suviroornporn P, et al. Detection of cardiac iron overload with native magnetic resonance T1 and T2 mapping in patients with thalassemia. Int J Cardiol 2017;248:421–6.
**ABSTRACT**

Imaging the heart is central to cardiac phenotyping, but in clinical practice, this has been restricted to macroscopic interrogation. Diffusion tensor cardiovascular magnetic resonance (DT-CMR) is a novel, noninvasive technique that is beginning to unlock details of this microstructure in humans in vivo. DT-CMR demonstrates the helical cardiomyocyte arrangement that drives rotation and torsion. Sheetlets (functional units of cardiomyocytes, separated by shear layers) have been shown to reorientate between diastole and systole, revealing how microstructural function facilitates cardiac thickening. Measures of tissue diffusion can also be made: fractional anisotropy (a measure of myocyte organization) and mean diffusivity (a measure of myocyte packing). Abnormal myocyte orientation and sheetlet function has been demonstrated in congenital heart disease, cardiomyopathy, and after myocardial infarction. It is too early to predict the clinical importance of DT-CMR, but such unique in vivo information will likely prove valuable in early diagnosis and risk prediction of cardiac dysfunction and arrhythmias. (J Am Coll Cardiol Img 2020;13:1235–55) © 2020 by the American College of Cardiology Foundation.

Myocardial phenotyping is crucial to understand the healthy heart and changes in disease. It offers insight into the cardiac structure–function relationship and is key to diagnosis, prognosis, and determining therapeutic interventions. However, phenotyping with current imaging techniques is limited to a scale of millimeters, and it is not possible to assess the microstructure of the myocardium without resorting to biopsy. Diffusion tensor cardiovascular magnetic resonance (DT-CMR) is a novel tool that provides noninvasive in vivo microstructural assessment, offering information at the scale of cardiomyocyte organization (Central Illustration). Preliminary studies have shown DT-CMR can identify unknown microstructural derangements in cardiomyopathy, myocardial infarction (MI), and congenital heart disease. Hence, there is increasing interest in its potential clinical usefulness and the new insight it brings to the pathophysiology of cardiac disease. This clinical review describes the cardiac microstructure, the DT-CMR technique, clinical studies performed so far, and the potential future role of DT-CMR.

**THE CARDIAC MICROSTRUCTURE**

**CARDIOMYOCYTES.** Cardiomyocytes measure approximately 150 by 20 μm and intercalate with several other cardiomyocytes (1). Although their branching nature means that cardiomyocytes do not strictly...
align in fibers, there is a directional grain to their appearance (Figure 1). This has led to variable terminology, when some use “fiber” to mean cardiomyocytes or groups of cardiomyocytes. Here, the phrase “cardiomyocyte orientation” is used to avoid confusion with the more strictly fiber-like skeletal muscle. In the left ventricle (LV), cardiomyocytes have a left-handed (LH) helical course at the epicardium, progressing through to a circumferential course in the mesocardium and then a right-handed (RH) helical course in the endocardium, as shown in the historical sequential dissection plates in Figure 1. Recently, histology by Streeter et al. (2) demonstrated the transmural variation of the fiber angle known as α. This angle, measured in the plane parallel to the epicardium and relative to the LV long axis, is positive at the endocardium and negative at the epicardium, reflecting RH and LH helical orientation, respectively (Figure 2). The near-zero α in the mesocardium indicates circumferential cardiomyocytes.

**SHEETLETS.** Cardiomyocytes are aggregated to form secondary structures, termed “sheetlets” (Figure 3). Each sheetlet is approximately 4 cardiomyocytes thick, surrounded and interconnected by the collagenous perimysium, allowing shear between neighboring sheetlets during the dynamic motion of cardiac contraction (3). It was initially believed that sheetlets formed stacked sheets, each extending the width of the LV wall (4). It is now appreciated that there are multiple local subpopulations containing counter-sloping sheetlets (5).

**STRUCTURE–FUNCTION RELATIONSHIP.** The myocardial microstructure is crucial to the dynamics of LV function. The helical arrangement of cardiomyocytes drives myocardial rotation and torsion (6). The dominant effect of the larger epicardial radius means that cardiomyocyte shortening of the LH epicardial cardiomyocytes leads to net clockwise rotation basally and anti-clockwise rotation apically, when viewed from the apex (6).

However, what is far less well appreciated is the contribution of sheetlets to cardiac function. Both Streeter et al. (2) and Spotnitz et al. (7) noted the “wall thickening paradox” in which cardiomyocyte thickening of only 8% could not explain wall thickening of 40%. Histological analysis in rat and dog myocardium suggested the concept of sheetlet rearrangement from a more LV epicardial wall parallel orientation in diastole to a more wall perpendicular arrangement in systole to facilitate LV wall thickening (4,7). However, until the advent of DT-CMR, there was no way of assessing in vivo microstructural changes through the cardiac cycle. Recent in vivo human and animal work strongly supported the concept of sheetlet reorientation as an important, if not the dominant, myocardial dynamic associated with radial thickening (8). There is still limited understanding of how myocyte shortening translates into the microstructural rearrangement that causes wall thickening. However, approaches such as DT-CMR should yield insight into this problem.

**CMR TECHNIQUE**

The theory and underlying methods behind diffusion MR were developed in the 1960s by Stejskal and Tanner (9) and advanced in the 1990s (10). The first clinical application of diffusion imaging was in neurology, where it was used for the early diagnosis of stroke (11). Cardiac diffusion imaging is considerably more difficult due to the bulk motion of the heart, but Edelman et al. (12) were able to overcome this by using a stimulated echo acquisition mode (STEAM) technique to produce the first in vivo diffusion cardiac image in 1994.

**DIFFUSION.** Diffusion imaging assesses diffusion of water. Free diffusion, when water molecules may diffuse in all directions equally, is known as isotropic diffusion. However, in the myocardium where cardiomyocytes and connective tissues act as barriers, diffusion is restricted (impermeable barriers) or hindered (permeable barriers), becoming anisotropic (Figure 4). DT-CMR exploits the effects of the microstructure on diffusion to yield information about the underlying myocardial organization.

**DIFFUSION-WEIGHTED CMR.** Diffusion is measured by assessing the signal loss between 2 images: a reference image and a main image with a higher degree of diffusion weighting. The weighting is applied by diffusion encoding gradients and described by the b-value, which encompasses gradient amplitude, duration, and temporal separation of the gradient pulses, and is quoted in units of seconds per square millimeter (10). Typically, values of 450 to 600 s/mm² are used (8,13,14). At higher b-values, the signal intensity is less easily distinguished from background noise (15). At lower b-values, other sources of diffusion-like intravoxel incoherent motion, including perfusion, confound the signal attenuation (16). The measured diffusion is known as the apparent diffusion coefficient (ADC) to accommodate factors, such as perfusion and hindered and/or restricted diffusion that impair accurate measures of
The fact that diffusion yields directional information was developed from the observation that ADC was higher when the diffusion gradient direction was aligned with the axonal direction in neurological diffusion imaging. The modern approach to determining microstructural orientations uses diffusion gradients applied in at least 6 directions. Information from the diffusion-weighted images is used to determine a diffusion tensor, which is a mathematical extension of a vector, having a 3-dimensional magnitude and direction.
ACQUIRING DT-CMR DATA. One method to acquire DT-CMR data is a spin echo (SE) sequence, known as the Stejskal-Tanner sequence (9). An excitation pulse is followed by a diffusion gradient that causes spin dephasing relative to position along the gradient. Application of a 180° refocusing pulse and a second diffusion gradient will realign the spins of static tissue to an equal but opposite net magnetization vector. For spins within a steadily flowing medium, this pulse sequence will lead to a net phase shift. However, in diffusion imaging, the random movement of the diffusing spins results in phase dispersion within each voxel. The vector sum of the spins in the presence of phase dispersion leads to decreased net magnetization, and thus signal loss (Figure 5). Diffusivity can be calculated from signal loss and diffusion weighting using the Stejskal-Tanner equation (9).

The key limitation of basic SE is cardiac motion that occurs during diffusion weighting, which is approximately 3 orders of magnitude greater than the distances diffused by water molecules and leads to large artefactual signal dropout. This was first addressed by bipolar diffusion gradients that offered first-order motion (constant velocity) compensation (20). Second- and third- (acceleration and jerk) order motion compensation techniques were then developed, although these require high performance gradient systems (Figure 6A) (14,21,22). Third-order motion compensation addresses the more complex diastolic motion, but requires longer echo times, so second-order motion compensation (M2-SE) is considered optimal. Thus, M2-SE data are typically acquired in systole (23,24). Validation using in vivo and post-mortem M2-SE DT-CMR in pigs has shown good levels of agreement (25). An M2-SE approach is
attractive and growing in popularity because of the higher signal-to-noise ratio than alternative methods, its suitability for free-breathing acquisition, and its more efficient whole heart coverage. It has been used in several initial human studies (14,22,26,27). A variation on M2-SE is a diffusion prepared method that allows a flexible choice of image acquisition (22).

A leading alternative sequence type is STEAM, and this addresses bulk motion artefact by splitting the 180° pulse into 2 90° pulses, so that the time over which diffusion is measured (\(\Delta\)) is an RR interval, and each image is acquired over 2 cardiac cycles (Figure 6B). Data acquisition is synchronized so that the heart is in the same position when both diffusion gradients are applied, thus minimizing the effects of cardiac motion. STEAM has been the mainstay of recent clinical DT-CMR studies because it does not require specialist hardware or motion compensation. Since its initial success in producing diffusion-weighted CMR images, STEAM has been readily applied to DT-CMR in both healthy and diseased hearts (8,12,28–30). However, the wide applicability of STEAM is offset by several disadvantages. It has low signal-to-noise ratio, requires 2 regular RR intervals per image, which necessitates longer
breath-holding or a navigator-led approach, and excludes patients with arrhythmias (31). Another disadvantage of STEAM in measuring diffusion is the effect of strain.

**THE CONFOUNDING EFFECTS OF STRAIN.** Strain, a measure of myocardial deformation, has been proposed as a confounder of DT-CMR results (28,32). Myocardial deformation occurs during the diffusion time of both sequences, but the longer diffusion time in STEAM makes its effects more significant. Reese et al. (32) originally described this phenomenon, explaining how tissue compression, in the direction of and following the initial STEAM gradient phase encoding, would have the effect of increasing the spatial modulation frequency and signal attenuation, and hence, ADC. An alternative simplified visual representation of how strain affects diffusion measures is shown in Figure 7. Diffusion within a medium that is compressed and then stretched back to its original state results in protons that travel further away from the starting point compared with the stationary case, thus overestimating diffusivity. Several correction methods for STEAM sequences exist, including bipolar gradients (33) or acquiring data at the “sweet spot,” the time-point where the effects of the strain history over the cardiac cycle are nulled (34). A post-processing correction technique uses macroscopic strain data (35). However, although strain has been considered a significant confounder to DT-CMR findings for many years (especially systolic secondary vector angulation [E2A] and E2A mobility), 2 recent studies have shown strain has only a limited effect and that uncorrected in vivo DT-CMR data are more representative of ex vivo findings (8,36). Consequently, the dynamic, laminar, and semi-permeable nature of the myocardium means strain has a complex, but limited effect on measured diffusion and requires further study (29,36,37).

**ANALYZING THE DATA.** The eigensystem. The 3-dimensional diffusion described by a tensor can be pictorially represented. Although isotropic diffusion in an unrestricted environment is a sphere, the restricted diffusion in the heart is an ellipsoid (Figure 8). The lengths of the 3-dimensional axes of the ellipsoid are labeled $\lambda_1$, $\lambda_2$, $\lambda_3$ (eigenvalues) in order of magnitude of diffusion, and their directions are E1, E2, and E3 (eigenvectors), respectively.

**Eigenvectors.** The eigenvectors can be projected onto cardiac planes (Figure 9), and several validation studies support the correspondence of E1 with average intravoxel cardiomyocyte orientation, E2 with the predominant sheetlet orientation, and E3 with the sheetlet normal direction (Supplemental Table 1) (5,8,38-43).

**Helix angle.** The primary eigenvector, the long axis of the diffusion ellipsoid, is projected onto the
The circumferential-longitudinal plane and reflects the mean intravoxel cardiomyocyte orientation (8,28,39). The angulation created by the projected primary eigenvector and the circumferential direction is $E_{1A}$ but is often described as the helix angle (HA) or $\alpha$ in some older published data. HA changes only a little during cardiac contraction (8).

Transverse angle. The transverse angle (TA) or imbrication angle reflects the tilt of the mean cardiomyocyte orientation toward and/or away from the central LV axis. It is derived by projecting $E_1$ into the circumferential-radial plane and then calculating the angle with the circumferential direction (38,43).

Secondary eigenvector angulation. The secondary eigenvector is projected onto the cross-myocyte plane (Figure 9). The angulation between $E_2$ projected into this plane and the myocyte perpendicular direction is termed $E_{2A}$ and is an index of sheetlet orientation (8). Unlike $E_{1A}$, $E_{2A}$ orientation changes substantially between systole and diastole. This change is called $E_{2A}$ mobility and reflects sheetlet function (8).

Tertiary eigenvector angulation. The tertiary eigenvector angulation ($E_{3A}$) is perpendicular to the sheetlet plane. $E_3$ is projected onto the longitudinal-radial plane and is positive when directed apico-basally (upward).

Mean diffusivity. In DT-CMR, mean diffusivity (MD) is derived from the tensor (19). It is the mean of $\lambda_1$, $\lambda_2$, and $\lambda_3$ and measured in units of square millimeters per second. MD reflects the packing and integrity of the myocytes, with low values indicating tight packing. MD rises with interstitial abnormality (e.g., fibrosis) because water has more freedom to diffuse (26,44). MD is similar to the mean ADC from diffusion-weighted CMR.

Fractional anisotropy. Fractional anisotropy (FA) is a scalar value reflecting the degree, but not direction, of anisotropy. Isotropic diffusion has an FA value of 0, and diffusion restricted to a single direction has a value of 1 (Figure 10). FA reflects the degree of
organization of a tissue, such that a higher value is more organized. Thus, a low FA might be expected with myocyte disarray, should it occur at an appropriate value relative to pixel size.

**VISUALIZING DT-CMR FINDINGS.** Tractography provides 3-dimensional visualization, typically tracking E1 across voxels into a smooth trajectory. In reality, this is a simplification because the myocardium does not contain serially aligned cardiomyocytes. Another representation uses superquadric glyphs, which are 3-dimensional bricks derived from the tensor that convey pixelwise information about the shape and orientation of the eigensystem (45). The orientation and size of the 3 axes of the glyphs represent the eigenvectors and eigenvalues, respectively.

**LIMITATIONS OF DT-CMR.** Acquiring and interpreting DT-CMR data is hampered by technical issues (46). Success rates for image acquisition vary by sequence type and cardiac phase and can be affected by factors such as mis-triggering and cardiac and respiratory motion (24). Scan times can be lengthy due to multiple acquisitions in different directions.

DT-CMR is limited in both spatial and angular resolution. Current in vivo spatial resolution is typically 2.7 × 2.7 mm² × 6 mm for M2-SE and 2.8 × 2.8 mm² × 8 mm for STEAM (8,14). Each DT-CMR image voxel contains millions of cardiomyocytes and many sheetlets. These are not uniformly aligned, and counter-orientated subpopulations exist (5). DT-CMR techniques are not able to resolve multiple populations within a single voxel, so the derived values reflect averages. It is also possible that partial volume effects may be responsible. Techniques such as de-noising and different k-space trajectories may aid reducing voxel size but help preserve the signal-to-noise ratio.

**DT-CMR OF THE HEALTHY HEART**

Clinical applications of DT-CMR are in relative infancy, but the unique ability to provide in vivo
microstructural information noninvasively has led to some describing it as “virtual histology.” The techniques are in constant evolution, and although measurement of myocyte and sheetlet orientations are reproducible and stable, the more global measures such as FA and MD show variation with technical sequence parameters and acquisition, mostly due to the varying diffusion times (24,27).

DIFFUSIVITY PARAMETERS. MD and FA are commonly reported DT-CMR parameters but vary depending upon sequence type, cardiac phase, and b-value (24,47,48). In vivo human studies comparing M2-SE and STEAM report higher MD and lower FA using M2-SE (24,27). This result is expected because with a shorter diffusion time, water molecules encounter fewer restrictive barriers (24,27). Reported values for MD and FA are provided in Supplemental Table 2. MD and FA tend to be provided as global values, usually across a mid-ventricular slice. However, regional differences have been described: FA peaks in the mesocardium (0.46 ± 0.04), compared with the endocardium (0.40 ± 0.04) and epicardium (0.39 ± 0.004), possibly due to the relative plateau in HA due to the circumferentially oriented mesocardial cardiomyocytes (48). For MD, there is a transmural gradient with an MD of 0.87 ± 0.07 × 10^{-3} mm^2/s at the epicardium that increases to 0.91 ± 0.08 × 10^{-3} mm^2/s in the endocardium. This may relate to the laminar structure of the myocardium, because sheetlets are increasingly prevalent toward the endocardium (49).

CARDIOMYOCYTE ORIENTATION. Various DT-CMR studies identify the transmural HA gradient in cardiomyocyte orientation (Supplemental Table 1) and report only minor changes in cardiomyocyte orientation toward a more longitudinal systolic orientation, as shown in Figure 12 (8,35,50). The transverse angle lies in the region of −20° to +20°, at both cardiac phases (43).

Deformation of an isotropic substance over the diffusion time affects the measured diffusion result. In the top panel, a systolic measurement is affected by the intervening diastolic stretch, and in the bottom panel a diastolic measurement is affected by the intervening systolic compression. For both, the diffusion pattern is ovoid in shape, rather than the expected isotropic sphere. Reprinted with permission from Ferreira et al. (36).
SHEETLET ORIENTATION. E2A is used as a DT-CMR index of sheetlet orientation, although E3 is used by some investigators. E2A changes substantially through the cardiac cycle (8). Figure 13 shows how sheetlets adopt a wall parallel sheetlet orientation in diastole (blue), which becomes more wall perpendicular in systole (red). This reorientation is intimately linked to the generation of radial strain. A small movement in the longitudinal direction translates into a larger radial expansion, similar to the perpendicular amplification action of a “lazy tong” (Supplemental Ref. 1). This is demonstrated by glyphs in Figure 13 and shown in Video 1. Biphasic differences in E2A have been described; a STEAM study of healthy humans reported diastolic E2A of 26° ± 6° and systolic E2A of 54° ± 6°, with E2A mobility of 27° ± 8° (51). A different STEAM study using E3A reported sheet angles of 65° ± 3.6° and 41.6° ± 3.7° in diastole and systole, respectively (35).

MICROSTRUCTURAL CHANGES IN CARDIAC DISEASE

MI. DT-CMR has been applied in MI, with much interest in acute changes and post-infarct ventricular remodeling. Several animal and human studies describe increased MD and decreased FA in the infarct zone (26,52–55). This accords with myocyte swelling and necrosis, extracellular matrix expansion, and replacement by less organized collagenous fibrosis. Ex vivo porcine DT-CMR 13 weeks after iatrogenic MI revealed increased mean ADC (1.01 ± 0.100 × 10⁻³ mm²/s) compared with control subjects (0.671 ± 0.106 × 10⁻³ mm²/s; p < 0.001) in the infarct zone (55). FA was significantly reduced in the infarct from 0.32 ± 0.01 to 0.20 ± 0.03 (p < 0.001). In the human study by the same group 26 days post-MI, DT-CMR detected increased mean ADC, decreased FA, and decreased RH and increased LH helical structures (cardiomyocytes) compared with the remote zone.
The follow-up human study at a median 191 days after MI described an increased proportion of RH cardiomyocytes in the remote zone, which correlated with increased wall thickness ($r = 0.66; p = 0.005$) and increased wall thickening in the adjacent zone ($r = 0.61; p = 0.01$) (56). The proposed explanation was that loss of RH cardiomyocytes fits with susceptibility of the endocardium to ischemia and gain of LH cardiomyocytes in the infarct zone and RH cardiomyocytes in the remote zone were both adaptive remodeling responses.

Recently, a study of MI in mice, sheep, and humans introduced the tractographic propagation angle, defined as the angle between 2 adjacent primary eigenvectors along a given tract and a metric of myofiber curvature, as shown in Figure 14 (57). A propagation angle value of 4° was reported as the threshold for differentiating normal from infarcted myocardium, as correlated to late gadolinium imaging and endocardial voltage mapping. Understanding microstructural changes post-infarct could offer insight into the pathogenesis and prognostication of negative remodeling and arrhythmias.

HCM. A microscopic hallmark of HCM is cardiomyocyte disarray, detectable currently only by histology. It is hoped that DT-CMR might detect disarray noninvasively, aiding diagnostic differentiation from HCM phenocopies and potentially identify those at higher risk of arrhythmias. A study of 5 patients suggested DT-CMR appeared to detect disarray by reduced FA and lower strain in the septum compared with the free wall of patients with HCM and 5 healthy control subjects (58). A reproducibility study in HCM reported regional differences where FA was lowest and MD highest in the septum,
although only the latter was significant (59). Although this might be related to septal hypertrophy and expanded extracellular space due to fibrosis and disarray, technical factors such as spatial variation in the signal-to-noise ratio might also be responsible; histological validation was absent. A preliminary study suggested FA was focally reduced in patients with HCM compared with control subjects and that DT-CMR might be able to detect myocardial disarray (60).

Diffusion-weighted CMR can offer another type of myocardial characterization in HCM. In a study of 23 patients with HCM, mean ADC was elevated in areas of fibrosis and correlated with extracellular volume ($r^2 = 0.72$), which suggested that diffusion-weighted CMR might detect the extent of fibrosis without a contrast agent (Figure 15) (44). However, in vivo DT-CMR demonstrated an entirely novel abnormality in HCM. Diastolic E2A was significantly elevated, and E2A mobility was reduced (Figure 16) (29). The failure of sheetlets to return to a more wall parallel orientation in diastole could be described as a failure of diastolic relaxation. Interestingly, this microstructural abnormality builds upon our knowledge of HCM pathophysiology, in which sarcomeric mutations may result in increased myofilament sensitivity to calcium, increasing relative cardiomyocyte tension (Supplemental Ref. 2).

DILATED CARDIOMYOPATHY. Dilated cardiomyopathy DCM has also been studied using DT-CMR. A SE study of hamsters with DCM found no change in HA or TA, but elevated MD and reduced FA compared with control hamsters (Supplemental Ref. 3). An in vivo STEAM study of 9 patients with nonischemic DCM and control subjects found MD was similar between groups and cardiac phases (30). FA was lower in patients with DCM compared with control subjects (diastole $0.56 \pm 0.07$ vs. $0.63 \pm 0.05$; $p < 0.04$, and systole $0.58 \pm 0.08$ vs. $0.62 \pm 0.07$; $p = 0.56$). The transmural HA gradient in diastole was steeper in patients with DCM, although this difference seemed to be driven by 2 patients. There was systolic HA redistribution in control subjects, with the expected more longitudinal orientation, but this was not seen in patients with DCM. E2A findings are shown in Figure 17. Biphasic E2A changes in control subjects (Figures 17A and 17C) showed predominance of low diastolic E2A and a broader systolic distribution.
However, there was relatively little change in the E2A distribution for patients with DCM (Figures 17B and 17D). The findings of this study must be tempered by its limitations; only 9 patients without LV dilatation and with strain correction, which may have obscured, had altered sheetlet mobility.

Nielles-Vallespin et al. (8) studied patients with DCM and HCM, and control subjects and did not use strain correction. They found similar HA distributions in the 3 cohorts. HA shifted toward more longitudinal in systole for all groups. Diastolic E2A was similar between groups, but systolic E2A findings were abnormal in patients with DCM. In control subjects, median systolic (interquartile range) E2A was 65° (6°), and in patients with HCM, it was 74° (7°). In patients with DCM, systolic E2A was significantly reduced at 40° (16°), yielding a reduced E2A mobility and impaired sheetlet mobility (Figure 18). Both radial and circumferential strains were significantly and similarly reduced in the cardiomyopathy groups compared with control subjects. However, the range of E2A (low to low in DCM and high to high in HCM) provided mechanistic insight into these findings. This study was limited by the mean ejection fraction...
Fraction (EF) in the DCM group of 45 ± 11%, with approximately one-half of the patients having only mild LV impairment. However, despite this, the altered sheetlet behavior was statistically significant.

Having established microstructural abnormalities in DCM, the same group studied patients with recovered DCM and compared them to patients with DCM and healthy control subjects (61). The patients were defined by LV size and EF entirely within indexed reference ranges and New York Heart Association functional class I. Again, there was little difference in the HA histograms among the 3 cohorts, but significant findings were present in E2A. Diastolic E2A was similar among groups. However, systolic E2A in those with recovered DCM was 59° (14°), which was significantly greater than the DCM group (35° [17°]; p < 0.0001), but lower than the control subjects (65° [8°]; p = 0.01). When E2A mobility was plotted against the EF, patients with recovered DCM and control subjects were indistinguishable by EF but could be discriminated by E2A (Figure 19).
Together, these 2 studies suggest that DT-CMR can detect impaired sheetlet behavior in dilated cardiomyopathy that appears to persist even when LV size and EF recover to normal by conventional measures.

**CONGENITAL HEART DISEASE.** There is a paucity of DT-CMR data in congenital heart disease. In an adult with transposition of the great arteries corrected by arterial switch, DT-CMR showed predominance of longitudinal and oblique fibers in the systemic right ventricle, which is believed to be an adaptive response to the systemic pressure and load (Supplemental Ref. 4). A larger study of 12 patients with situs inversus totalis, 12 healthy situs solitus control subjects, and 2 ex vivo situs inversus totalis hearts showed deranged cardiomyocyte orientation, sheetlet abnormalities, and functional impairment in situs inversus totalis (62). All situs solitus hearts displayed the expected helical arrangement. By contrast, in situs inversus totalis, HAs were more heterogeneous, both intrasubject and intersubject. However, the general pattern was an inverted HA arrangement at the base, with positive HAs in the epicardium and negative HAs in the endocardium, whereas toward the apex, the transmural HA distribution was more similar to situs solitus. There was a mid-ventricular transition zone. These findings were confirmed in the ex vivo hearts. Mid-LV peak radial and circumferential strain were reduced, and overall absolute torsion was significantly reduced in situs inversus totalis. This was the first in vivo demonstration of substantial departure from the typical mammalian helical cardiomyocyte arrangement (Figure 20). In addition to the abnormal cardiomyocyte arrangement in situs inversus totalis, there was also impaired sheetlet mobility with failure to achieve the expected systolic orientation. This might reflect cardiomyocyte derangement that affected the transverse shears that were integral to sheetlet reorientation (6). These findings reinforced the connection between the microstructure and cardiac mechanics. The abnormal cardiomyocyte structure in situs inversus totalis raises the question of whether such patients might have a greater susceptibility to heart failure with a “second hit” to

In hypertrophic cardiomyopathy, the apparent diffusivity coefficient (ADC) is elevated in regions of fibrosis, as detected by late gadolinium enhancement (LGE) and increased extracellular volume (ECV). Reprinted with permission from Nguyen et al. (44)
FUTURE DIRECTIONS OF DT-CMR

DT-CMR can identify microstructural changes in disease. Further work is required to broaden the applicability and usefulness of the technique. Two main streams of future development are needed: technical and clinical. Technical developments would address spatial and angular resolution, scan acceleration, increased coverage, and refining the understanding of strain effects. Clinical

---

Example E2A maps of a mid-ventricle slice. The healthy control subject has a blue (low E2A) map in diastole and a red (higher E2A) map is systole. In hypertrophic cardiomyopathy (HCM), maps are predominantly red, displaying elevated E2A at both cardiac phases. The plot below shows that diastolic E2A is significantly elevated compared with the healthy control subjects, as is systolic E2A. Adapted with permission from Ferreira et al. (29). Abbreviation as in Figure 13.
development might see DT-CMR playing a role as a diagnostic and prognostic tool. The ability to detect microstructural changes before manifest disease expression may offer a role for earlier diagnosis of cardiomyopathies. It may also help identify patients at risk of developing heart failure, not only in cardiomyopathy, but also congenital and ischemic heart disease. DT-CMR may inform the debate on whether patients with DCM whose EF is improving have achieved recovery or remission. In HCM, the ability (if possible in the future) to detect disarray in vivo could assist risk stratification for predicting sudden cardiac death. Similarly, identifying those at risk of potentially life-threatening arrhythmias after infarction is another area in which DT-CMR has the potential to offer novel

**FIGURE 17** E2A Findings in Dilated Cardiomyopathy

(A and B) E2A histograms for control subjects and patients with dilated cardiomyopathy. Diastolic and systolic distributions are shown by solid and dashed lines, respectively. (C and D) Change from the expected computer model results. Reprinted with permission from von Deuster et al. (30).
Sheetlet planes are defined by the primary and secondary eigenvectors (E1 and E2). Septal glyphs are shown, color-coded according to absolute E2A (blue towards wall-parallel and red towards wall-perpendicular). Healthy control subjects show a more wall-parallel alignment in diastole and more wall-perpendicular alignment in systole. However, in HCM, sheetlets retain the more wall-perpendicular arrangement of systole in both cardiac phases. Conversely, in dilated cardiomyopathy (DCM), the more wall-parallel arrangement of diastole persists in both cardiac phases. Replotted from Nielles-Vallespin et al. (8). Abbreviation as in Figure 16.
Secondary eigenvector (E2A) mobility plotted against left ventricle ejection fraction (LVEF). Patients with DCM patients have low LVEF and low E2A mobility. Both control subjects and recovered DCM groups have normal EF, but the recovered DCM group can be discriminated by their significantly lower E2A mobility. Reprinted with permission from Khalique et al. (61). Abbreviations as in Figures 13 and 18.

LV tractography of a situs solitus (SS) and situs inversus (SIT) heart. The contrast between the left-handed helix (blue) in the SS heart, and the right-handed helix (red) in the SIT heart is particularly striking. Modified with permission from Khalique et al. (62).
HIGHLIGHTS

- DT-CMR is a unique technique for noninvasive assessment of myocardial microstructure.
- DT-CMR has identified novel cardiomyocyte and sheetlet abnormalities in cardiac disease in vivo.
- DT-CMR has the potential to aid clinical diagnosis and risk stratification through microscopic phenotyping.

CONCLUSIONS

DT-CMR is establishing itself as a technique that can interrogate the cardiac microstructure and its relation to function. For the first time, it is possible to assess cardiomyocyte and sheetlet structure and microstructural dynamics using a noninvasive approach. DT-CMR provides insight into pathological changes in disease, and, with this new understanding, it has the potential to progress to a clinically useful tool aiding diagnosis and prognosis, as well as guiding patient management.

REFERENCES

1. Opie LH, Bers DM. Mechanisms of cardiac contraction and relaxation. In: Mann DL, Zipes DP, Libby P, Bonow RO, editors. Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine. 10th Edition. Philadelphia, PA: Elsevier Saunders, 2015; p 429-53.
2. Streeter DD, Spotnitz HM, Patel DP, Ross J, Sonnenblick EH. Fiber orientation in the canine left ventricle during diastole and systole. Circ Res 1969;24:339-47.
3. LeGrice IJ, Smail BH, Chai LZ, Edgar SG, Gavin JB, Hunter PJ. Laminar structure of the heart: ventricular myocyte arrangement and connective tissue architecture in the dog. Am J Physiol Heart Circ Physiol 1995;269:H571-82.
4. LeGrice IJ, Takayama Y, Covell JW. Transverse shear along myocardial cleavage planes provides a mechanism for normal systolic wall thickening. Circ Res 1995;77:182-93.
5. Kung G, Nguyen TC, Itch A, et al. The presence of 2 local myocardial sheet populations confirmed by diffusion tensor MRI and histological validation. J Magn Reson Imaging 2011;34:1080-91.
6. Young AA, Cowan BR. Evaluation of left ventricular torsion by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012;14:49.
7. Spotnitz HM, Spotnitz WD, Cottrell TS, Spiro D, Sonnenblick EH. Cellular basis for volume related wall thickness changes in the rat left ventricle. J Mol Cell Cardiol 1974;6:317-31.
8. Nielles-Vallespin S, Khalique Z, Ferreira PF, et al. Assessment of myocardial microstructural dynamics by in vivo diffusion tensor cardiac magnetic resonance. J Am Coll Cardiol 2017;69:661-76.
9. Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. J Chem Phys 1965;42:288-92.
10. Le Bihan D, Turner R, Moonen CTW, Pekar J. Imaging of diffusion and microcirculation with gradient sensitization: design, strategy, and significance. J Magn Reson Imaging 1991;1:7-28.
11. Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. Neurology 1992;42:1717-23.
12. Edelman RR, Gao J, Wedeen VJ, et al. In vivo measurement of water diffusion in the human heart. Magn Reson Med 1994;32:423-8.
13. Scott AD, Ferreira PFAD, Nielles-Vallespin S, et al. Optimal diffusion weighting for in vivo cardiac diffusion tensor imaging. Magn Reson Med 2015;74:420-30.
14. Stoeck CT, von Deuster C, Genet M, Edelman RR. Fast magnetic resonance diffusion-tensor imaging. Magn Reson Med 2007;57:331-7.
15. Basser PJ, Baylan K, Magrath K, Emns DB. Quantifying precision in cardiac diffusion tensor imaging with second-order motion-compensated convex optimized diffusion encoding. Magn Reson Med 2018;80:1074-87.
16. Nguyen C, Fan Z, Xie Y, et al. In vivo diffusion-tensor MRI of the human heart on a 3 tesla clinical scanner: an optimized second order (2M) motion compensated diffusion-preparation approach. Magn Reson Med 2016;76:1534-63.
17. Walsh CL, DiBella EVR, Hsu EW. Higher-order motion-compensation for in vivo cardiac diffusion tensor imaging in rats. IEEE Trans Med Imaging 2015;34:1843-53.
18. Scott AD, Nielles-Vallespin S, Ferreira PF, et al. An in-vivo comparison of stimulated-echo and motion compensated spin-echo sequences for 3 T diffusion tensor cardiovascular magnetic resonance at multiple cardiac phases. J Cardiovasc Magn Reson 2018;20:1.
19. Stoeck CT, von Deuster C, Fleischmann T, Lipinski M, Cesarovic N, Kozerke S. Direct comparison of in vivo versus postmortem second-order motion-compensated cardiac diffusion tensor imaging. Magn Reson Med 2018;79:2265-76.
20. Nguyen C, Fan Z, Xie Y, et al. In vivo contrast free chronic myocardial infarction characterization using diffusion-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2014;16.
21. van Deuster C, Stoeck CT, Genet M, Atkinson D, Kozerke S. Spin echo versus stimulated echo diffusion tensor imaging of the in vivo human heart. Magn Reson Med 2016;76:862-72.
22. Reese TG, Weisskoff RM, Smith RN, Rosen BR, Dinsmore RE, Wedeen VJ. Imaging myocardial fiber architecture in vivo with magnetic resonance. Magn Reson Med 1995;34:786-91.
23. Ferreira PF, KLiner PJ, McGill L-A, et al. In vivo cardiovascular magnetic resonance diffusion tensor imaging shows evidence of abnormal myocardial laminar orientations and mobility in
hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2014;16:87.
30. von Deuster C, Sammut E, Asner L, et al. Studying dynamic myofiber aggregate reorientation in dilated cardiomyopathy using in vivo magnetic resonance diffusion tensor imaging. Circ Cardiovasc Imaging 2016;9:e005018.
31. Nielles-Vallespin S, Mekkaoui C, Gatehouse P, et al. In vivo diffusion tensor MRI of the human heart: reproducibility of breath-hold and navigator-based approaches. Magn Reson Med 2013;70:454-65.
32. Reese TG, Wedeen VJ, Weisskoff RM. Measuring diffusion in the presence of material strain. J Magn Reson B 1996;112:253-8.
33. Dou J, Reese TG, Tseng W-YI, Wedeen VJ. Cardiac diffusion MRI without motion effects. Magn Reson Med 2002;48:105-14.
34. Tseng W-YI, Reese TG, Weisskoff RM, Brady TJ, Wedeen VJ. Cardiac diffusion tensor MRI in vivo without strain correction. Magn Reson Med 1999;216:393–403.
35. Stoeck CT, Kalinowska A, von Deuster C, et al. Dual-phase cardiac diffusion tensor imaging with strain correction. PLoS One 2014;9:e107159.
36. Ferreira PF, Nielles-Vallespin S, Scott AD, et al. Evaluation of the impact of strain correction on the orientation of cardiac diffusion tensors with in vivo and ex vivo porcine hearts. Magn Reson Med 2017;79:2205–11.
37. Axel L, Wedeen VJ, Ennis DB. Probing dynamic myocardial microstructure with cardiac magnetic resonance diffusion tensor imaging. J Cardiovasc Magn Reson 2014;16:89.
38. Hales PW, Schneider JE, Burton RAB, Wright BJ, Bollensdorff C, Kohl P. Histographic structure of the living isolated rat heart in 2 contraction states assessed by diffusion tensor MRI. Prog Biophys Mol Biol 2012;109:319–30.
39. Scollan DF, Holmes A, Winslow R, Forder J. Histological validation of myocardial microstructure obtained from diffusion tensor cardiac magnetic resonance. Am J Physiol Heart Circ Physiol 1998;275:H1208–18.
40. Hsu EW, Muzikant AL, Matelevicis SA, Penland RC, Henriquez CS. Magnetic resonance myocardial fiber-orientation mapping with direct histological correlation. Am J Physiol Heart Circ Physiol 1999;276:H627–34.
41. Holmes AA, Scollan DF, Winslow RL. Direct histological validation of diffusion tensor MRI in formaldehyde-fixed myocardium. Magn Reson Med 2000;44:157–61.
42. Tseng W-YI, Wedeen VJ, Reese TG, Smith RN, Halpern EF. Diffusion tensor MRI of myocardial fibers and sheets: correspondence with visible cut-face texture. J Magn Reson Imaging 2003;17:31–42.
43. Chen J, Liu W, Zhang H, et al. Regional ventricular wall thickening reflects changes in cardiac fiber and sheet structure during contraction: quantification with diffusion tensor MRI. Am J Physiol Heart Circ Physiol 2005;289:H1898–907.
44. Nguyen C, Lu M, Fan Z, et al. Contrast-free detection of myocardial fibrosis in hypertrophic cardiomyopathy patients with diffusion-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2015;17:107.
45. Ennis DB, Kindlmann G. Orthogonal tensor invariants and the analysis of diffusion tensor magnetic resonance images. Magn Reson Med 2006;55:136–46.
46. Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. NMR Biomed 2010;23:803–20.
47. Tuncilliﬂe EM, Scott AD, Ferreira P, et al. Intercentre reproducibility of cardiac apparent diffusion coefﬁcient and fractional anisotropy in healthy volunteers. J Cardiovasc Magn Reson 2014;16:31.
48. McGill L-A, Scott AD, Ferreira PF, et al. Heterogeneity of fractional anisotropy and mean diffusivity measurements by in vivo diffusion tensor imaging in normal human hearts. PLoS One 2015;10:e0132360.
49. Pope AJ, Sands GB, Small BH, LeGrice IJ. Three-dimensional transmural organization of perimysial collagen in the heart. Am J Physiol Heart Circ Physiol 2008;295:H1243–52.
50. Mekkaoui C, Nielles-Vallespin S, Gatehouse PD, Jackowski MP, Firmin DN, Sosnovik DE. Diffusion MRI tractography of the human heart in vivo at end-diastole and end-systole. J Cardiovasc Magn Reson 2012;14:O49.
51. McGill LA, Ferreira PF, Scott AD, et al. Relationship between cardiac diffusion tensor imaging parameters and anthropometrics in healthy volunteers. J Cardiovasc Magn Reson 2016;18.
52. Wu M-T, Tseng W-YI, Su M-YM, Huang Y-L, et al. Sequential changes of myocardial microstructure in patients postmyocardial infarction by diffusion-tensor cardiac MR: correlation with left ventricular structure and function. Circ Cardiovasc Imaging 2009;2:32–40.
53. Mekkaoui C, Jackowski MP, Kostis WJ, et al. Myocardial scar delineation using diffusion tensor magnetic resonance tractography. J Am Heart Assoc 2018;7:e007834.
54. Tseng W-YI, Dou J, Reese TG, Wedeen VJ. Imaging myocardial fiber disarray and intramural strain hypokinesis in hypertrophic cardiomyopathy with MRI. J Magn Reson Imaging 2006;23:1–8.
55. McGill L-A, Ismail TF, Nielles-Vallespin S, et al. Reproducibility of in vivo diffusion tensor cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2012;14:86.
56. Ariga R, Tuncilliﬂe EM, Manohar SG, et al. Non-invasive imaging of myocardial disarray associates with ventricular arrhythmia in hypertrophic cardiomyopathy. Eur Heart J 2017;38.
57. Khalique Z, Ferreira PF, Scott AD, et al. Diffusion tensor cardiovascular magnetic resonance of microstructural recovery in dilated cardiomyopathy. J Am Coll Cardiol Img 2018;11:1548–50.
58. Khalique Z, Ferreira PF, Scott AD, et al. Deranged myocyte microstructure in situ vs. in vitro cardiac magnetic resonance. J Am Coll Cardiol Img 2018;11:1360–2.

KEY WORDS cardiomyocytes, diffusion tensor CMR, helix angle, microstructure, sheetlets

APPENDIX For supplemental references, a table, and videos, please see the online version of this paper.
ABSTRACT
Since its inception in 2008, JACC: Cardiovascular Imaging (JACC) has served as an important publication for all contemporary aspects of cardiovascular imaging. Understanding the dissemination trends in cardiovascular imaging has traditionally been evaluated through citations that assess interest in the research community. Recently, social media, alternative metrics (Altmetrics), and other modern metrics have enabled a more broader understanding of the interests of clinical readership. Through the prism of Altmetrics, this review discusses the most impactful studies across the spectrum of cardiovascular imaging within and outside of JACC during a 3-year period (2017 to 2019). The top 100 Altmetrics JACC articles in this timeframe, included articles with the highest impact with the combination of high Altmetrics (median: 66; interquartile range [IQR]: 56 to 108), high citations (median: 26; IQR: 17 to 34), and high downloads (median: 9,626; IQR: 5,770 to 11,435). This review aims to provide a framework to understand how to incorporate these metrics for a modern approach to dissemination of knowledge in the field of cardiovascular imaging.

(J Am Coll Cardiol Img 2020;13:1256–69) © 2020 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.
“Simplicity is triumphing over complexity, accessibility is beating exclusivity, the power is increasingly in the hands of the user.”

—Chandrashekhar and Narula quoting Eric Schmidt of Google (1)

Since its inception in 2008, JACC: Cardiovascular Imaging (iJACC) has served as an important publication for all contemporary aspects of cardiovascular imaging. The journal has continually introduced the latest advances in publishing for engaging reader experience. iJACC has tried to successfully adapt to the rise of social media (SoMe) for dissemination of cardiovascular imaging knowledge by enabling simplicity, accessibility, and usability via SoMe platforms—reaching viewers beyond traditional online and in-print platforms (Central Illustration, Figure 1) (2). This review aims to complement some of the other journal content to demonstrate how SoMe and other modern metrics serve the interests of the readership (3,4). It also provides a framework (Central Illustration) to understanding how to incorporate these metrics for dissemination of knowledge in the field of cardiovascular imaging (5).

SOCIAL MEDIA

Traditionally, a key metric of relevance for medical journals has been the power of the Impact Factor, which is a tool that primarily focuses on citation numbers. Because an accurate portrait of citations in published work only emerges after several years, this metric does not represent a full assessment of the early impact on readership (6,7). Thus, the use of Alternative Metrics is an emerging, complementary approach. (2). Termed “Altmetrics,” these bibliometrics, as assessed by organizations such as Plum Analytics and Altmetrics.com, allow for measurement of real-time impact of publications through attention to scholarly outputs in nontraditional sources, including news articles, SoMe, and blogs. Through Altmetrics, article dissemination can be tracked, and impact on readership of iJACC through shares, retweets, digital impressions, and comments generated. SoMe may also enhance a journal’s exposure, create awareness of newly published work, and perhaps most importantly, rapidly communicate this knowledge to the readership.

The Altmetrics Attention Score (AAS) is a metric that measures the total weighted count of the online attention of a published journal article. Some studies have shown that the SoMe promotion strategy is associated with higher readership and downloads, although a 2015 randomized trial showed no effect (8,9). Correlation between the AAS score and citations have been modest but have also been stronger when assessing the early impact of clinical trials or meta-analyses (9,10). The “knowledge chunks” derived from SoMe may further drive post-peer review discussion among the cardiovascular imaging, cardiovascular, and general medical readership within SoMe, which can further propel the publication cycle by generating novel ideas and potentially new collaborations (Figure 2).

In a detailed review of the top 100 Altmetrics iJACC articles over the past 3 years, the SoMe editors of iJACC (A.D.C., J.B.G.) qualitatively noted several relevant factors for AAS and citations (Table 1, Figure 3). The highest AAS and cited articles have been the publication of the highest quality, novel, prospective clinical studies that are either relevant to daily clinical practice or foundational to further research. Although examining the link between AAS and citations alone from iJACC demonstrates low to modest correlation (2), further stratifying highly cited articles alone from iJACC demonstrates low to modest correlation (2), further stratifying highly cited articles into the top and bottom one-half of AAS scores led to several interesting observations (Table 2). Of the top 100 Altmetric articles, 40% of these iJACC articles were shared directly by the JACC SoMe accounts, which to date have >30,000 followers on Twitter and 111,000 followers on Facebook. Another 18% were shared by an individual, Professor M.A. Garcia Fernandez (@Maeco-cardio) of the Spanish Cardiac Imaging Society, who as of this writing has >10,000 followers on Twitter. Articles are often shared by authors, key opinion leaders, recognized thought leaders in the field, and/or SoMe influencers in a uniquely flattened SoMe hierarchy that allows for interaction across the spectrum of cardiovascular medicine.

However, although a high follower base provides an important means for attention, it alone may not reflect traditional scholarly leadership, defined by metrics such as the H-index or clinical reputation. According to Twitter, high Altmetrics articles were found to have an upper bound reach of followers of >159,000, which resulted from the amplification effect of tweets and retweets (Table 1). In addition, early editorial board identification of key advances in the field that led to timely review articles with actionable, novel clinical knowledge both received significant attention and became highly cited. Articles that received both low attention and low citations

| ABBREVIATIONS AND ACRONYMS |
|-----------------------------|
| 3D = 3-dimensional          |
| AAS = Altmetrics Attention Score |
| AS = aortic stenosis        |
| CAC = coronary artery calcium |
| CAD = coronary artery disease |
| CMR = cardiac magnetic resonance |
| FFR = fractional flow reserve |
| iJACC = JACC: Cardiovascular Imaging |
| LGE = late gadolinium enhancement |
| LV = left ventricle         |
| LVEF = left ventricular ejection fraction |
| PET = positron emission tomography |
| SoMe = social media         |

AND ACRONYMS |
#JACCIMG Social Media Temporal Trends and a Conceptual Framework of Attention Versus Citations

**A**

Temporal trends in JACC: Cardiovascular Imaging (JACC) social media postings on Twitter (#JACCIMG) that include tweets, retweets, and image and article postings from January 2017 through December 2019.

**B**

Conceptual framework of Altmetrics attention versus citations in cardiovascular (CV) imaging. Articles are categorized as: 1) high-attention, low citation, termed as "shared broadly"; 2) high-attention, high citation, termed as "shared broadly and cited"; 3) low-attention, low citation, termed as "quietly published"; and 4) low attention, high citation, termed as "shared and cited" with general observations included within the figure. 3D = 3-dimensional; AS = aortic stenosis; CAC = coronary artery calcium; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; ECV = extracellular volume; LFLG = low-flow, low gradient; MR = magnetic resonance; NICM = nonischemic cardiomyopathy.
were generally less downloaded (Table 1). There was no imaging modality-specific trend identified between high and modest Altmetrics articles. Thus, in providing a framework of impact of Altmetrics versus citations through all 804 *iJACC* articles from 2017 to 2019, we suggest these 4 general categories: “shared broadly”; “shared broadly and cited”; “shared and cited”; and “quietly published” (Figure 3). The highest-impact articles were those that were both shared broadly and cited, whereas articles shared broadly also demonstrated readership impact.

Determining the long-term scientific merit of high Altmetrics articles bears further analysis (2). For example, the top Altmetrics article in *iJACC* of 2019, an intriguing research letter by Khanji et al. (11) (Altmetrics: 308) evaluated the association between recreational cannabis use and cardiac structure by cardiovascular magnetic resonance (CMR). Here, the investigators found a significantly increased left ventricular volume and impaired strain in cannabis users using data from the United Kingdom Biobank. The Twitter attention was broad, and several major news outlets discussed this letter because of the

---

**FIGURE 1** Analysis of Altmetrics Attention Score and Number of Tweets From *iJACC* Articles

![Graph showing total Altmetrics score and number of tweets from 2017 to 2019. The total Altmetrics score and number of Twitter posts from 2017 to 2019 show steadily rising engagement over this time period. *iJACC* = *JACC: Cardiovascular Imaging.*](image)

---

**FIGURE 2** Conceptual Model of Publication Cycle and Impact in CV Imaging

![Diagram showing the publication cycle, including peer review, editorial review, publication, dissemination, and various metrics like Altmetric score, downloads, and citations.](image)

---

After imaging research, the publication cycle includes peer-review, editorial review, and finally publication. Social media and Altmetrics enable an understanding of the initial (weeks to months) impact of an article, which may have influence on downloads and citations that are measures of impact that become known after months to years. CV = cardiovascular.
TABLE 1 Analysis of Altmetrics Attention Score and Citations From iJACC 2017 to 2019

| Altmetric Top 100 vs. All Other Articles | High Altmetrics, High Citation (n = 29) | High Altmetrics, Low Citation (n = 27) | Moderate Altmetrics, High Citation (n = 22) | Moderate Altmetrics, Low Citation (n = 22) | All Others (n = 704) |
|-----------------------------------------|----------------------------------------|---------------------------------------|--------------------------------------------|------------------------------------------|---------------------|
| Altmetric score                         | 66 (56–108)                            | 73 (58–90)                            | 36 (33–40)                                 | 34 (30–45)                               | 5 (1–14)            |
| Citations                               | 26 (17–34)                             | 4 (3.5–6)                             | 14 (10–29)                                 | 3 (1–5)                                 | 4 (1–13)            |
| Downloads                               | 9,626 (5,770–11,435)                   | 4,132 (2,363–5,799)                   | 5,524 (3,998–7,382)                        | 1,832 (923–3,202)                       | 493 (272–878)*      |
| Twitter retweets                        | 116 (89–186)                           | 118 (86–142)                          | 52 (40–66)                                 | 36 (10–56)                              | 8 (1–29)            |
| Twitter upper bound followers           | 244,031 (181,654–317,270)              | 178,807 (118,598–270,042)             | 124,529 (82,842–154,591)                   | 70,392                                   | N/A                 |
| Cardiac imaging subspecialty            |                                       |                                       |                                            |                                          |                     |
| Echocardiography                        | 16 (57)                                | 16 (59)                               | 10 (45)                                    | 8 (36)                                   | N/A                 |
| Nuclear cardiology                      | 1 (3)                                  | 2 (7)                                 | 2 (9)                                      | 0 (0)                                    | N/A                 |
| Cardiac CT                              | 11 (38)                                | 11 (41)                               | 7 (32)                                     | 7 (33)                                   | N/A                 |
| CMR                                     | 6 (27)                                 | 12 (44)                               | 5 (23)                                     | 3 (14)                                   | N/A                 |
| Invasive imaging                        | 1 (4)                                  | 1 (4)                                 | 5 (23)                                     | 3 (14)                                   | N/A                 |
| Multimodality                           | 6 (27)                                 | 9 (33)                                | 6 (27)                                     | 3 (14)                                   | N/A                 |
| Study type                              |                                       |                                       |                                            |                                          |                     |
| Original research                       | 19 (66)                                | 7 (26)                                | 16 (73)                                    | 7 (33)                                   | N/A                 |
| Review paper                           | 8 (28)                                 | 13 (48)                               | 5 (23)                                     | 4 (19)                                   | N/A                 |
| Editorial                               | 1 (3)                                  | 2 (7)                                 | 0 (0)                                      | 5 (24)                                   | N/A                 |
| Letter/iMail                            | 1 (3)                                  | 2 (7)                                 | 1 (5)                                      | 2 (9)                                    | N/A                 |
| Case/iPix                               | 0 (0)                                  | 3 (11)                                | 0 (0)                                      | 4 (19)                                   | N/A                 |
| JACC Journals social media main influencer | 11 (39)                              | 6 (22)                                | 14 (64)                                    | 7 (33)                                   | N/A                 |

Values are median (interquartile range) and n (%). Papers published in iJACC were stratified into those with the top 100 Altmetric Attention scores versus all other publications. The top 100 Altmetrics papers were then divided into the top and bottom one-half (high altmetrics vs. modest altmetrics) as well as top and bottom one-half of citations (high citation, low citation). Within the top 100 Altmetrics, the generally highest observed downloads were for papers with high altmetrics and high citations. High altmetrics, low citation, and moderate altmetrics, high citation articles had the next highest level of downloads. All others had the lowest range of downloads, were rarely posted on social media, and had generally lower citations. *Downloads data listed through February 2019 for this cell.

CT = computed tomography; CMR = cardiac magnetic resonance.

lifestyle-oriented subject matter, giving an alternative portrait of its societal impact. However, limitations of unmeasured confounders, uncertain mechanisms, and long-term prognostic data suggested that the long-term scientific merit was less certain, and therefore, it might receive a lesser degree of citations.

To measure the impact of SoMe in cardiovascular imaging requires evaluating the complementary role of hashtags in tracking the impact of specific topics (Table 2). The hashtag, specifically introduced by the octothorpe symbol (#), is a metadata tag that allows users to search for all posts tagged with that message. Tracking the most relevant SoMe hashtags in imaging reveals tens of millions to hundreds of millions of estimated digital impressions from thousands of global participants online (Table 2).

**PROS AND CONS OF SOCIAL MEDIA ENGAGEMENT.** There are pros and cons to consider in SoMe engagement in works of demonstrable academic merit. Highly cited articles not disseminated via a SoMe portal have been noted by the iJACC editorial team to have less SoMe opportunity for discussion (Figure 3). In a world where many clinical teams are on SoMe to get rapid access to knowledge before print (online before print), this race to the first knowledge of new publications does not completely equate to the impact factor. Nuances of the culture of the SoMe crowd that encompass social and emotional capital may be difficult to quantify but represent an important appreciable factor in knowledge dissemination. SoMe influencers may guide Altmetric trends by discussing publications influenced by an individual’s own practice environment, visual appeal, or even simply attention for its own sake. In addition, negative attention to an article may be weighted similarly to positive attention by Altmetrics, making the appropriate scientific merit of a paper confounded. In this vein, online engagement may generate a “boomerang” effect with an unintended and unpredictable response. Negative attention may be unsolicited and lacking appropriate nuance.

With these factors in mind, it raises the question of how iJACC should best measure the broad-ranging and valuable “wisdom of the SoMe crowd” (12) with the expertise of a highly experienced editorial board and accomplished peer-review community; these are not mutually exclusive entities. iJACC, which is uniquely positioned as an international, trusted hub.
of cardiac imaging, has a natural interface with the visual-driven aspects of SoMe that enables a high degree of engagement.

**HIGH ATTENTION IMAGING ARTICLES ACROSS CARDIOVASCULAR MEDICINE.** The studies with the most attention within clinical cardiovascular imaging have evaluated imaging approaches with clinical outcomes in stable coronary artery disease (CAD) ([Central Illustration](#)). Because a detailed review of these studies has been discussed within these pages and elsewhere, this review will briefly touch upon the SoMe impact of these studies. The SCOT-Heart (Scottish Computed Tomography of the Heart) 5-year study demonstrated that computed tomography angiography (CTA), in addition to standard care, resulted in significantly reduced death or nonfatal myocardial infarction at 5 years (13). This study was already highly influential according to both traditional metrics (n = 149) and by AAS (Altmetrics: 690). This score was significantly higher than the index paper (Altmetrics: 192) published in the *Lancet* in 2015 (14). Factors for this difference include: 1) increased attention through SoMe; 2) simultaneous SoMe and news coverage at the European Society of Cardiology Congress; and 3) the important positive finding that demonstrated, for the first time, that an imaging strategy showed improved outcomes in a randomized trial.

The tension between Altmetrics attention and scientific merit may be best exemplified in the recent uptick in cardiovascular imaging papers that use machine learning algorithms. A recently published paper that evaluated the radiomic features of adipose tissue fibrosis through the perivasculatenual fat attenuation index from cardiac CTA in the SCOT-Heart trial was found to improve major adverse cardiovascular event(s) prediction beyond traditional risk factors, coronary artery calcium (CAC) score, stenosis, and high-risk plaque features. This *European Heart Journal* publication had an Altmetric score of 853,
TABLE 2 Hashtag Trends in Cardiovascular Imaging Social Media

| Hashtag      | Registration Date | Total Tweets† (thousands) | Total Retweets (thousands) | Total Participants (thousands) | Digital Impressions‡ (millions) | Visuals§ (thousands) | Papers |
|--------------|-------------------|---------------------------|---------------------------|--------------------------------|---------------------------------|---------------------|--------|
| #JACCIMG     | 1/1/2017          | 7.9                       | 7.2                       | 2.5                            | 40.2                            | 7.9                 | 7.7    |
| #ACCImaging  | 3/30/2017         | 16.0                      | 13.3                      | 3.3                            | 42.6                            | 14.6                | 4.8    |
| #EchoFirst   | 11/20/2017        | 123.9                     | 105.8                     | 16.1                           | 220.4                           | 116.7               | 20.1   |
| #YesCCT      | 8/2/2019          | 1.4                       | 0.92                      | 0.32                           | 3.1                             | 1.5                 | 0.36   |
| #CVImaging   | 4/1/2016          | 28.2                      | 22.7                      | 5.0                            | 65.0                            | 30.8                | 8.1    |
| #CVNuc       | 8/2/2019          | 8/11/2018                 | 12.5                      | 17.4                           | 3.8                             | 62.9                | 23.7   |
| #WhyCMR      | 4/1/2016          | 28.2                      | 22.7                      | 5.0                            | 65.0                            | 30.8                | 8.1    |
| #ISCHEMIA    | 10/14/2019        | 11.0                      | 8.2                       | 4.2                            | 37.4                            | 7.2                 | 2.7    |

An analysis of tweets, participants, and digital impressions of the most widely-used cardiovascular imaging hashtags. Data from Symplur signals (78). †Registration date reflects the date the hashtag was registered with symplur.com. Individual hashtag data are from the registration date to access on December 31, 2019. ‡The total number of unique tweets since the hashtag was registered on symplur.com. §Impressions are computed by taking the number of times an account has tweeted multiplied by the account’s number of followers repeated for all accounts, then finally summed up. ¶The total number of times each photo, GIF, or video was shared.

fueled by >100 news stories. However, it is uncertain whether this attention reflects rapid broad adoption of this technique, as well as a need for further external validation.

The magnetic resonance perfusion or fractional flow reserve (FFR) in coronary disease (MR-INFORM [The Myocardial Perfusion CMR versus Angiography and FFR to Guide the Management of Patients with Stable Coronary Artery Disease]) study found that use of stress perfusion CMR had a lower incidence of coronary revascularization than FFR, was noninferior to FFR with regard to major adverse events, and generated a significant impact on Twitter (Altmetric: 388).

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, which is not yet in fully published form as of this writing, has generated significant interest online after presentation at the recent American Heart Association Scientific Sessions. The hashtag #ISCHEMIA has already generated >30 million digital impressions alone across cardiovascular specialties and general medicine.

Hashtag topics of interest shared broadly should not be ignored. These include: 1) #ThePowerofZero, which is bringing attention to the role of zero CAC imaging for the prediction of cardiovascular events (15–18); 2) #CardsRads, which discusses approaches to cardiology and radiology collaborations in advanced imaging (19); and 3) #Structural and #iEcho, which expand discussions around advocacy, clinical training, and reimbursement issues in this rapidly evolving field (20–22).

From this point forward, to appreciate the interests of the SoMe crowd while allowing the readership to better manage recent advances in the field, this review takes a topical and modality approach to discuss those articles that have garnered both the highest SoMe attention and highest citations over the past 3 years across cardiovascular imaging, with an emphasis on JACC.

ECHOCARDIOGRAPHY

HEART FAILURE. Transthoracic echocardiography offers the ability to assess measures of systolic function, diastolic function, and structural abnormalities (Supplemental Figure 1). Twitter discussion on identification of patients at risk for heart failure elevated the AAS of an investigation by Gong et al. (23) (Altmetrics: 27), which demonstrated that identification of at least 1 abnormal parameter in subjects with preclinical heart failure provided 72% to 82% sensitivity for detection of subsequent progression to overt symptomatic heart failure in subjects age 65 years or older. Echocardiographic epidemiological changes in left ventricular (LV) systolic dysfunction and heart failure within the Framingham Study over 3 decades garnered attention via news media, Twitter, and policy mentions, with a study by Vasan et al. (24) (Altmetric: 62) that noted trends toward lower prevalence of LV systolic dysfunction and increasing frequency of heart failure with preserved ejection fraction (EF). Cardiovascular mortality associated with heart failure with reduced LVEF declined across decades, whereas it remained unchanged for heart failure with preserved LVEF. Defining imaging features of heart failure with preserved LVEF remains a challenge and area of active Twitter discussion.

STRAIN IMAGING. A review of application of 2- and 3-dimensional (3D) strain imaging across cardiac health and disease was the highest Altmetric-rated imaging article during the study period, driven by robust Twitter discussion and a strong Central Illustration in
the study by Morris et al. (25) (Altmetric: 178). Left atrial strain imaging provided unique insights into diastolic dysfunction and might be a better barometer than left atrial size. In patients with elevated LV filling pressures, left atrial strain was more likely to be abnormal than the left atrial volume index (62.4% vs. 33.6%; \( p < 0.01 \)) (26) (Altmetric: 49). Furthermore, left atrial strain might serve to clarify the often convoluted assessment of LV diastolic function, because left atrial strain changes progressively with severity of diastolic function, unlike traditional parameters (27) (Altmetric: 50).

**Valvular Heart Disease.** There has been renewed interest in understanding predictors of mortality in asymptomatic severe aortic stenosis (AS). Although an LVEF cutoff of 60% has long been used in AS, new data suggest that an LVEF cutoff of 55% identifies worse outcomes in patients with severe AS and minimal or no symptoms, which sparked discussion on Twitter (28) (Altmetric: 51). Furthermore, a meta-analysis of asymptomatic patients with AS found that impaired global longitudinal strain was predictive of reduced survival in patients with normal LVEFs (29) (Altmetric: 59).

Echocardiographic assessment of ventricular heart disease presents unique difficulties. Traditional echocardiographic parameters may be insufficient for hemodynamic evaluation in the presence of valvular heart disease. In mitral annular calcification, the mitral E/e' ratio should not be used to estimate LV filling pressures, whereas the mitral E/A ratio and isovolumic relaxation time are useful predictors (30). This research was among the 10 highest AAS studied (Altmetric: 139), driven by a combination of Facebook and Twitter discussions. Evaluation of mitral regurgitation is dependent upon etiology. El Sabbagh et al. (31) (Altmetric: 116) noted that primary and secondary mitral regurgitation represented 2 completely different diseases, with separate natural histories, mechanisms, therapeutic strategies, and outcomes associated with repair. Grayburn et al. (32) (Altmetric: 144) generated attention via news media and Twitter by proposing division of secondary mitral regurgitation into “proportionate” or “disproportionate” on the basis of the ratio of effective regurgitant orifice area and LV end-diastolic volume.

**3-Dimensional Echocardiography.** Topics about 3D echocardiography are of high interest on SoMe. Three-dimensional imaging continues to be at the forefront of innovation, spanning improved techniques for chamber quantification, novel cardiac valve visualization, structural planning, 3D printing, and translation to virtual reality (33,34) (Altmetric: 84, Lang et al.). Three-dimensional echocardiography has also helped to clarify paradoxical annular dynamics with systolic expansion and flattening of mitral annular dysfunction in mitral valve prolapse (34).

**Nuclear Cardiology and Health Policy**

**Novel Imaging Techniques.** Online discussion and enthusiasm have been substantial for several papers that described novel nuclear imaging techniques. Dweck et al. (35) (Altmetric: 55) conducted a small cohort study that evaluated a hybrid of CMR and positron emission tomography (PET) for diagnosing active sarcoidosis within the myocardium (Supplemental Figure 2). The study evaluated 25 subjects with suspected cardiac sarcoidosis and demonstrated how simultaneous acquisition of the 2 imaging modalities could effectively distinguish patients with active and inactive sarcoidosis, as well as prove absence of cardiac involvement and false-positive PET from insufficient glucose uptake suppression. Online, many retweeted the notice about the article from @JACCJournals and further discussion revolved around cardiologists sharing with one another about the importance of avoiding false-positive diagnoses. Massera et al. (36) (Altmetric: 8) conducted a study in 27 patients with AS that compared 2 software packages for quantifying activity of valve calcification. The methods they applied are being developed as possible outcomes for new pharmacological strategies to reduce progressive calcification of cardiac valves. In addition to discussion on Twitter, this paper was selected for further review on the podcast for the *Journal of Nuclear Cardiology* (37), which regularly has 200 to 300 listeners for each episode.

A well-designed randomized comparative effectiveness study by Patel et al. (38) from September 2019 evaluated the impact of stress myocardial perfusion imaging plus PET versus single-photon emission computed tomography and found no differences in the rate of diagnostic failure, angiography, revascularization, or health status at 1 year, although the study was underpowered. Downstream invasive testing with PET myocardial perfusion imaging was more consistent with high-risk features. The low AAS of 2 masked the importance of this underused study design, underappreciating the multiple advantages of PET myocardial perfusion imaging in myocardial blood flow quantification, and perhaps reflecting bias against negative study results.
PATIENT SAFETY: REDUCING RADIATION. As one of the imaging modalities that uses ionizing radiation, reducing patient radiation exposure is a focus of the nuclear cardiology community. One of the most recent and widely discussed articles on this topic is a review article by Williams et al. (39) (Altmetric: 95). The review summarized important terminology and practical strategies on how physicians and technologists can effectively make imaging safer. The article was discussed on the Heart journal podcast (40) and generated numerous tweets from physicians encouraging the conscientious use of imaging with radiation. Thompson et al. (41) (Altmetric: 38) published a research letter in JACC on how their nuclear cardiac laboratory was able to substantially reduce the effective doses received by patients over an 8-year time frame (Supplemental Figure 2). This was accomplished with the acquisition of more efficient cameras, upgrades to software, and redesigned, patient-focused imaging protocols. Although published as a research letter, the high Altmetric score for this paper was driven by news coverage from several outlets, including TCTMD.

HEALTH POLICY. In 2014, the United States government passed a law changing how the Medicare system would reimburse advanced imaging technologies, including nuclear, CT, and CMR, with echocardiography exempt. Since that time, the responsible federal agencies have been working to implement the new system that will require clinicians to reference appropriate use criteria when ordering any noninvasive imaging test. The program has been repeatedly delayed, but the current “go-live” date is January 1, 2021. Because of the many challenges that the program creates for both ordering clinicians and those who provide advanced imaging services, many articles have been written to coach teams on how to be ready for adoption and also asking for additional reprieve and leniency from the government. One such editorial by Doukky et al. (42) (Altmetric: 94) makes the case for collaboration between academic and private practices, observing that efforts to reduce low-value care are a shared responsibility of all physicians and cardiovascular team members.

ATHEROSCLEROSIS, PERFUSION, AND CALCIUM IMAGING BY CARDIAC CT

CARDIAC CTA EVALUATION OF PLAQUE MORPHOLOGY AND PROGRESSION. Developments in CCTA for improved assessment of atherosclerosis, prognostication, and in guiding management developed high interest within the readership (Supplemental Figure 3). A substudy of the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial in JAMA Cardiology evaluated high-risk plaque features (positive remodeling, low attenuation, or napkin ring sign) and found these features had independent risk prediction among patients with nonobstructive CAD, younger patients, and women (43) (Altmetric: 108). To demonstrate CT use beyond risk prediction to CT evaluation of treatment response, as shared by influencers, @JACCJournals and @jvillacastin, a prospective multinational observational registry, PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging), evaluated patients with suspected or known CAD who underwent serial cardiac CTA (44) (Altmetric: 97). This study divided patients into statin-naïve and statintaking patients. Through a model of CT quantification, statins were associated with slower progression of noncalcified plaque but increased calcified plaque components (44).

A highly provocative study shared by @JACCJournals and @BinitaShahMD (Altmetric: 143) that evaluated the effects of colchicine and optimal medical therapy on atherosclerotic plaque in patients with recent acute coronary syndrome found significant reductions on serial cardiac CTA in low-attenuation plaque volume and high-sensitivity C-reactive protein. The SoMe response included how this data supported anti-inflammatory strategies (Supplemental Figure 3).

The safety and yield of a selective referral versus direct referral strategy through the CONSERVE (CCTA for Selective Cardiac Catheterization) study received significant SoMe attention from throughout the cardiovascular community (45) (Altmetric: 160). Through a noninferiority study design, a selective referral strategy through cardiac CTA was similarly effective for the diagnosis of CAD, whereas the cardiac CTA strategy reduced invasive catheterization by 77%, with an estimated 57% reduction diagnostic cost.

CAC IMAGING. Deepening understanding of CAC progression through a review of noninvasive, invasive, and histological approaches captured SoMe interest (Supplemental Figure 4) (46) (Altmetrics: 67). CAC was classified as intimal and mediastinal calcification with a specific focus on intimal thickening. The investigators reviewed the effect of sex on atherosclerosis development and the protective effect of estrogen in delaying progression in women. The review also discussed using the subtype of calcium (small, fragmented, spotty) as a better predictor of stable plaque compared with heavy calcium (diffuse, fibrocalcific plaques, sheet of calcium).
A paper by Nakahara et al. (47) (Altmetric: 69) complemented the preceding paper by reviewing the molecular mechanisms belying CAC. Imaging of microcalcification through 18F-NaF discussed in this article led to several subsequent research studies with increasing uptake. To expound further on patients with CAC ≥1,000, a study published by Peng et al. (48), which was presented at the American College of Cardiology 2019 Scientific Sessions, evaluated 66,636 asymptomatic adults from the CAC consortium and found that this phenotype was associated with mortality similar to high-risk secondary prevention cohorts. SoMe coverage of the American College of Cardiology presentation and simultaneous publication in iJACC served to elevate the paper to an Altmetric score of 94 (Supplemental Figure 4).

A research letter that evaluated severe CAC in South Asians from the MASALA (Mediators of Atherosclerosis in South Asians Living in America) study was highly shared on SoMe, driven by the large number of news articles (n = 11), particularly from Asian news outlets (49) (Altmetric: 122). In this work, the presence of a family history of heart disease was independently associated with high CAC burden (CAC >300). Finally, a paper by Miname et al. (50) (Altmetric: 86) that evaluated CAC and cardiovascular events in patients with familial hyperlipidemia generated significant SoMe attention. This study demonstrated potential heterogeneity in atherosclerosis manifestation in patients with zero events in the CAC = 0 population and high-risk patients in the CAC >100 population. The SoMe interest was driven in part by discussion around the hashtag #ThePowerofZero.

CARDIOMYOPATHIES, CAD, AND VALVULAR DISEASE BY CMR

CARDIOMYOPATHIES. Myocardial tissue characterization with CMR opened a window to noninvasively assess features of diseased myocardium previously restricted to histology (Supplemental Figure 5). Among the highest attention iJACC articles was a paper by Halliday et al. (51) that evaluated the relationship between late gadolinium enhancement (LGE) and dilated cardiomyopathies. When the study stratified LGE into categories of 0% to 2.55%, 2.55% to 5.1%, and >5.1%, the hazard ratios ranged from 2.79 to 4.87 for the 3 groups, with the greatest sudden cardiac death risk in the septum and free wall. A review paper by Patel and Kramer (52) (Altmetric: 75) emphasized the role of CMR in nonischemic cardiomyopathies; in dilated cardiomyopathy, the presence and burden of LGE helped risk stratify for sudden cardiac death (53). The presence of LGE in hypertrophic cardiomyopathy was not enough to prognosticate, but the extent, location, and/or pattern were more important to predict adverse outcomes (54). In sarcoidosis, the presence of LGE had great prognostic value, but could not identify earlier clinical stages, which might be possible by T2 mapping (55). In cardiac amyloidosis, the presence of transmural LGE was associated with >5-fold increase in mortality (56). Both native T1 mapping and extracellular volume fraction were shown to be prognostic in this condition.

CAD. Within iJACC, the article with the highest attention in the area of CAD and CMR was a study by Dastidar et al. (58) (Altmetric: 114) that evaluated CMR in myocardial infarction with normal coronary arteries (MINOCA). In this case, the Altmetric score was driven by Twitter, with both @JACCJournals and the investigators themselves posting, including senior author Dr. Chiara Bucciarelli-Ducci (@chiarabd). In this cohort of MINOCA (myocardial infarction with normal coronary arteries) patients, 74% had a definitive diagnosis (25% myocarditis, 25% myocardial infarction, and 25% cardiomyopathy) with cardiomyopathy demonstrating the highest mortality followed by those with myocardial infarction. A group from the University of Ulm in Germany presented a randomized clinical trial (n = 200) of patients with symptomatic CAD who underwent direct invasive coronary angiography or stress CMR with adenosine (Supplemental Figure 5) (59) (Altmetric: 32). They found that the CMR group had a lower rate of revascularization versus the rate of the angiography group, without differences in outcomes (59).

VALVULAR HEART DISEASE. In the field of valvular heart disease, CMR offers accurate volumetric and hemodynamic assessments, with myocardial tissue characteristics that give insight on myocardial health. A state-of-the-art review led by Marwick et al. (60) (Altmetric: 50) presented a summary of the data for...
assessment of subclinical myocardial dysfunction in AS using echocardiographic and CMR techniques (Supplemental Figure 5). The important prognostic role of LGE and T1 mapping in AS, despite normal LVEF, was established (61,62). The currently most studied CMR parameter in AS has been LGE, which has been consistently prognostic (63). This area of research holds promise for CMR tissue characterization becoming part of the assessment and decision-making of asymptomatic severe AS.

CARDIO-ONCOLOGY

Cardio-oncology clinical studies allow insight with regard to cardiovascular outcomes in cancer patients as influenced by risk factors, associated procedures, additional diagnoses, and current real-life clinical practices (64–66). For example, the CECCY (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity) trial found a low incidence (1% in the placebo group) of LV systolic dysfunction in a cohort of 200 patients with breast cancer who received treatment with anthracycline and who were randomized to either preventive treatment with carvedilol or placebo (67).

Beyond monitoring cardiotoxicity of anthracycline and trastuzumab toxicity, a state-of-the-art paper on multimodality imaging in oncology patients by Plana et al. (68) (Altmetric: 48) emphasized not only the role of echocardiography and strain to identify cardiotoxicity, but how other modalities might contribute significantly to the assessment of different clinical scenarios in patients with cancer. Cardiac CTA, nuclear stress modalities, and stress CMR can help identify significant CAD in patients undergoing cancer treatments that may cause ischemia (e.g., 5-fluoracil, capecitabine, bevacizumab, sorafenib, and sunitinib) (69). CMR tissue characterization has helped understanding of certain mechanistic aspects of chemotherapy-related cardiotoxicity, such as development of myocardial inflammation earlier and fibrosis later, but applications are still in the realm of research. Jordan et al. (70) (Altmetric: 80) presented a practical clinical review (Supplemental Figure 5) on the use of CMR in cardio-oncology.

STRUCTURAL HEART INTERVENTIONAL IMAGING

The field of structural heart interventional imaging has benefitted from SoMe, a forum that fills a critical need for rapid dissemination of knowledge in a dynamically changing field. SoMe has served not only to bring attention to the papers published, but also as a tool to advance and bridge knowledge gaps among barriers to access to care, new devices, and new imaging training platforms for all. Because of the broad published reports within structural interventional imaging, several review articles have had the highest Altmetrics impact. Because most clinical centers have limited access to first-in-man or novel clinical trial devices, a state-of-the-art paper by Hahn et al. (71) on the critical metrics guiding imaging know-how and requirements for investigational tricuspid annuloplasty devices (Trialign [Mitralign, Tewksbury, Massachusetts] and Cardioband [Edwards Lifesciences, Irvine, California]), leaflet devices (edge-to-edge and FORMA [Edwards Lifesciences, Irvine, California]), and transcatheter tricuspid valve replacements reached an Altmetrics score of 61 (Supplemental Figure 6). SoMe discussions on tricuspid interventions have triggered a new hashtag #TreatTR. Moving from the tricuspid valve to mitral valve, articles on methods and efficacy (72) (Altmetric: 76), patient selection, and periprocedural guidance (73) (Altmetric: 42) have been shared broadly.

Contrary to traditional academic publications, step-by-step tutorials and user guides are now leading the impact both clinically and by Altmetrics in structural interventional imaging. Bax et al. (74) illustrated the multimodality critical thinking required for transcatheter mitral repair and replacement approaches across various devices in their recent publication (Supplemental Figure 6). This review included devices focused on the leaflets (e.g., MitraClip [Abbott Laboratories, Abbott Park, Illinois]), annulus (e.g., Cardioband), and replacement (e.g., Intrepid TMVR [Medtronic, Minneapolis, Minnesota]).

Much of the role of imaging in transcatheter interventions is not only prevention of procedural complications, but in identification of challenging cases while also troubleshooting device success and failure. Pibarot et al. (74) (Altmetric: 71) demonstrated the role of multimodality thinking in providing accurate differential diagnosis for clinical teams troubleshooting symptoms of dyspnea in patients after aortic valve replacement (Supplemental Figure 6) and the role of having access to multiple imaging toolkits. A multimodality review of imaging for evaluation of the left atrial appendage presented an up-to-date complementary approach to planning and treatment of atrial fibrillation and appendage occlusion (75) (Altmetric: 52).

The value of structural heart interventional imaging providers in the success of transcatheter interventions has commonly been undervalued. A letter to the editor by Wang et al. (20) (Altmetric: 47) outlining the need for training and challenges in a career in structural imaging was accompanied by robust
SoMe discussions. Subsequent *iJACC*-commissioned editorial viewpoints on core competencies in cardiac CT (21) (Altmetric: 29) and transesophageal echocardiography in structural imaging (22) (Altmetric: 29) sparked ongoing efforts within the cardiovascular societies.

The future of structural heart interventional imaging is based on adaptation of new technology toolkits to enhance and improve existing clinical paradigms. A state-of-the art review by Vukicevic et al. (76) (Altmetric: 104) on cardiac 3D printing and its future directions was followed by original research by Qian et al. (77) (Altmetric: 203) on the application of 3D printing procedural simulation in predicting paravalvular leak after transcatheter aortic valve replacement. These papers consisted of new conceptual frameworks for novel technologies not common to modern clinical practice, with case examples demonstrating images in interventional planning and a multimodal approach to application of 3D printing in transcatheter interventions (76).

**CONCLUSIONS: FUTURE OF SOCIAL MEDIA AND CARDIOVASCULAR IMAGING**

Rather than seeking solely to answer or refute the question of post hoc ergo propter hoc between Altmetrics and citations, understanding the emergence of SoMe in cardiovascular imaging necessitates keeping the mission of *iJACC* at the core: the dissemination of novel advancement in imaging for the cardiovascular community. In 2018, *iJACC* made the conscious decision to become an online only journal, because 90% of the readership access content through online devices. Because digital media are at the vanguard of publishing, particularly in imaging, modern media, including SoMe, is a natural part of this evolutionary arc. At the same time, *iJACC* remains committed to serving as an avenue for novel, highest-quality, peer-reviewed papers. Because the impact factor remains a “curious and capricious metric” for the journal (5), the emergence of Altmetrics, SoMe shares, and hashtag impressions provide an evolving portrait of the readership. What is trending on SoMe may not always become scientifically impactful by citations (and not absent its own inherent risks and challenges; “moth to the flame?”) (2). Yet, assessing trends (Central Illustration) while keeping aim on lasting impact are not mutually exclusive but complementary goals. It is the goal of the authors of this paper that the conceptual framework (Central Illustration, Figure 2) presented may serve as a starting point for the cardiovascular community to best integrate these evolving measures of attention and citation. Lastly, *iJACC* aims to further tap into the unreached potential of SoMe to accelerate the translation of this research to global audiences. Join us by following the hashtag #JACCIMG in this digital (r)evolution!

**ACKNOWLEDGMENT** The authors thank Dr. Vishak Kumar for his initial review of the SoMe aspects of the Altmetrics data.

**ADDRESS FOR CORRESPONDENCE:** Dr. Andrew D. Choi, The George Washington University School of Medicine, 2150 Pennsylvania Avenue NW, Suite 4-417, Washington, DC 20037. E-mail: adchoi@gwu.edu. Twitter: @AChoiHeart, @JeffreyGeske, @RonBlankstein.

**HIGHLIGHTS**

- Understanding the relationship of the impact in cardiovascular imaging papers requiring the incorporation of Altmetrics, SoMe, and citation impact to assess for the early effects on readership.
- This review provides a framework to understand how these metrics enable knowledge dissemination through a discussion of the top topics across the field of cardiovascular imaging from 2017 to 2019.
- This novel framework of Altmetrics, SoMe, and citations may allow the cardiovascular community to further tap into the unreached potential of SoMe to accelerate the translation of future research to global audiences.

**REFERENCES**

1. Chandrareshkhar Y, Narula J. *iJACC* in the evolving world of integrated imaging: a spectator, a follower, or a trail blazer. *J Am Coll Cardiol Img* 2008;1:691-3.
2. Chandrareshkhar Y, Shaw L. Journal editors and altmetrics: moth to the flame? *J Am Coll Cardiol Img* 2019;12:1899-902.
3. Shaw L, Chandrareshkhar Y, *JACC*: Cardiovascular Imaging Editors. Progress in cardiovascular imaging. *J Am Coll Cardiol Img* 2019;12:2589-610.
4. Kramer CK, Shaw LJ, Chandrareshkhar Y, *JACC*: Cardiovascular Imaging Editors. Progress in cardiovascular imaging. *J Am Coll Cardiol Img* 2018;11:1883-914.
5. Parwani P, Choi AD, Lopez-Mattei J, et al. Understanding social media: opportunities for cardiovascular medicine. *J Am Coll Cardiol* 2019;73:1089-93.
6. Fuster V. Impact factor: a curious and capricious metric. *J Am Coll Cardiol* 2017;70:1530-1.
Cardiac Imaging and Modern Metrics

Choi AD, Feuchtner GM, Wein-McCall J, Shaw LJ, Min JK, Villines TC. Accelerating the future of cardiac CT: social media as sine qua non? J Cardiovasc Comput Tomogr 2020 Jan 31 [E-pub ahead of print].

Fox CS, Bonaca MA, Ryan JJ, Massaro JM, Barry K, Loscalzo J. A randomized trial of social media as sine qua non? J Am Coll Cardiol 2018;72:86-8.

Barakat AF, Nimri N, Shokr M, et al. Correlation of cardiac imaging and the prediction of heart failure progression in preclinical stage A/B subjects. J Am Coll Cardiol Img 2017;10:1504-19.

Vasan RS, Xanthakis V, Lyass A, et al. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham Study: an echocardiographic study over 3 decades. J Am Coll Cardiol Img 2018;11:1-11.

Voigt JU, Cvivic M, 2- and 3-dimensional myocardial strain in cardiac health and disease. J Am Coll Cardiol Img 2019;12:1849-63.

Morris DA, Belyavskiy E, Aravind-Kumar R, et al. Potential usefulness and clinical relevance of adding left atrial strain to left atrial volume index in the detection of left ventricular diastolic dysfunction. J Am Coll Cardiol Img 2018;11:1405-15.

Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA strain for categorization of LV diastolic dysfunction. J Am Coll Cardiol Img 2017;10:735-43.

Bohbott D, de Meester Ravenstein C, Chadhga G, et al. Relationship between left ventricular ejection fraction and mortality in asymptomatic and minimally symptomatic patients with severe aortic stenosis. J Am Coll Cardiol Img 2019;12:38-48.

Magne J, Cosyns B, Popescu BA, et al. Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic aortic stenosis: an individual participant data meta-analysis. J Am Coll Cardiol Img 2019;12:84-92.

Abdulab MM, Chebrolu LH, Schutt RC, Naghue SF, Zogbi WA. Doppler echocardiography for the estimation of LV filling pressure in patients with mitral annular calcification. J Am Coll Cardiol Img 2017;10:1411-20.

El Sabbagh A, Reedy YNV, Nishimura RA. Mitral valve regurgitation in the contemporary era: insights into diagnosis, management, and future directions. J Am Coll Cardiol Img 2018;11:628-43.

Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. J Am Coll Cardiol Img 2019;12:353-62.

Lang RM, Addetia K, Naran A, Mor-Avi V. 3-dimensional echocardiography: latest developments and future directions. J Am Coll Cardiol Img 2018;11:1854-78.

Lee AP, Jin CN, Fan Y, Wong RHL, Underwood MJ, Wan S. Functional implication of mitral annular disjunction in mitral valve prolapse: a quantitative dynamic 3D echocardiographic study. J Am Coll Cardiol Img 2017;10:1424-33.

Dweck MR, Abgral R, Trivieri MG, et al. Hybrid magnetic resonance imaging and positron emission tomography with fluorodeoxyglucose to diagnose active cardiac sarcoidosis. J Am Coll Cardiol Img 2018;11:94-107.

Maxsera D, Doris MK, Cadet S, et al. Analytical quantification of aortic valve 18F-sodium fluoride PET uptake. J Nucl Cardiol 2018 Nov 29 [E-pub ahead of print].

Heart BMJ Podcast – what cardiologists need to know. Available at: https://soundcloud.com/bmjpodcasts/radiation-what-we-need-to-know. Accessed January 4, 2020.

Thompson RC, O’Keefe JH, McGhie AL, Bybee KA, Thompson EC, Bateman TM. Reduction of SPECT MPI radiation dose using contemporary protocols and technology. J Am Coll Cardiol Img 2018;11:282-3.

Doukkly K, Diemer G, Medina A, et al. Promoting appropriate use of cardiac imaging: no longer an academic exercise. Ann Intern Med 2017;166:438-40.

Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. JAMA Cardiol 2018;3:144-52.

Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. J Am Coll Cardiol Img 2018;11:1475-84.

Chang HJ, Lin FY, Gebow D, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected CAD: a randomized, controlled, open-label trial. J Am Coll Cardiol Img 2019;12:1303-12.

Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: what does it really mean? J Am Coll Cardiol Img 2018;11:127-42.

Nakahara T, Dweck MR, Narula N, Pisapia D, Narula J, Strauss HW. Coronary artery calcification: from mechanism to molecular imaging. J Am Coll Cardiol Img 2017;10:582-93.

Peng AW, Mirbolouk M, Grimolone OA, et al. Long-term all-cause and cause-specific mortality in asymptomatic patients with CAC >1,000: results from the CAC Consortium. J Am Coll Cardiol Img 2020;13:83-93.

Patel J, Al Rifai M, CaiAZAhicharia M, et al. Family history of CHD is associated with severe CAC in South Asians: comparing the MSALAA and MESA studies. J Am Coll Cardiol Img 2017;10:958-60.

Miname MH, Bittencourt MS, Moraes SR, et al. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia.
receiving standard lipid-lowering therapy. J Am Coll Cardiol Img 2019;12:1797-804.

51. Halliday BP, Balse AJ, Gulati A, et al. Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. J Am Coll Cardiol Img 2019;12:1645-55.

52. Patel AR, Kramer CM. Role of cardiac magnetic resonance in the diagnosis and prognosis of non-ischemic cardiomyopathy. J Am Coll Cardiol Img 2017;10:1180-93.

53. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA 2013;309:896-908.

54. Chan RH, Maron BJ, Olivottio I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484-95.

55. Crouser ED, Oro C, Tran T, He X, Raman SV. Improved detection of cardiac sarcoidosis using magnetic resonance with myocardial T2 mapping. Am J Respiratory Critical Care Med 2014;189:109-12.

56. Fontana M, Pica S, Reant P, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2015;132:1570-9.

57. Aung N, Zemrau F, Mohiddin SA, Petersen SE. LV Noncompaction cardiomyopathy or just a lot of trabeculations? J Am Coll Cardiol Img 2017;10:704-7.

58. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with non-Q wave syndrome. J Am Coll Cardiol Img 2019;12:283-96.

59. Potts JE, Iliescu CA, Lopez Mattei JC, et al. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. Eur Heart J 2019;40:1790-800.

60. Bharadwaj A, Potts J, Mohamed MO, et al. Acute myocardial infarction treatments and outcomes in 6.5 million patients with a current or historical diagnosis of cancer in the USA. Eur Heart J 2019 Dec 4 [E-pub ahead of print].

61. Guha A, Buck B, Biersmith M, et al. Contemporary impacts of a cancer diagnosis on survival following in-hospital cardiac arrest. Resuscitation 2019;142:30-7.

62. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR, et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY Trial. J Am Coll Cardiol 2018;71:2281-90.

63. Plana JC, Thavendiranathan P, Bucsiarelli-Ducci C, Lancellotti P. Multi-modality imaging in the assessment of cardiovascular toxicity in the oncology patient. J Am Coll Cardiol Img 2018;11:1150-72.

64. Hahn RT, Nabauer M, Zuber M, et al. Intra-procedural imaging of transcatheter tricuspid valve interventions. J Am Coll Cardiol Img 2019;12:532-53.

65. Bax JJ, Debonnaire P, Lancellotti P, et al. Transcatheter interventions for mitral regurgitation: multimodality imaging for patient selection and procedural guidance. J Am Coll Cardiol Img 2019;12:2029-48.

66. Wunderlich NC, Beigel R, Ho SY, et al. Imaging for mitral interventions: methods and efficacy. J Am Coll Cardiol Img 2018;11:872-901.

67. Pibarot P, Magne J, Leipsic J, et al. Imaging for predicting and assessing prosthesis-patient mismatch after aortic valve replacement. J Am Coll Cardiol Img 2019;12:149-62.

68. Pathan F, Hecht H, Narula J, Marwick TH. Roles of transesophageal echocardiography and cardiac computed tomography for evaluation of left atrial thrombus and associated pathology: a review and critical analysis. J Am Coll Cardiol Img 2018;11:616-27.

69. Vukicevic M, Mosadegh B, Min JK, Little SH. Cardiac 3D printing and its future directions. J Am Coll Cardiol Img 2017;10:171-84.

70. Qian Z, Wang K, Liu S, et al. Quantitative prediction of paravalvular leak in transcatheter aortic valve replacement based on tissue-mimicking 3D printing. J Am Coll Cardiol Img 2017;10:719-31.

71. Symplur Signals. Available at: https://www.symplur.com. Accessed January 4, 2020.

**KEY WORDS** Altmetrics, cardiac computed tomography, cardiac magnetic resonance, echocardiography, interventional cardiology, medical publishing, nuclear cardiology, social media, structural

**APPENDIX** For supplemental figures, please see the online version of this paper.
IMAGING VIGNETTES

PET/CMR

One More Step Toward Noninvasive Morphofunctional Diagnosis of Cardiac Malignancies

Soraya El Ghannudi, MD, PhD,a,b,c Philippe Germain, MD,b Gerlinde Averous, MD,d,e Afshin Gangi, MD, PhD,b,e Thomas H. Schindler, MD, PhD,f Alessio Imperiale, MD, PhDa,e,g

CARDIAC MALIGNANCIES ARE RARE, INCLUDING PRIMARY AND METASTATIC NEOPLASMS DEVELOPING either by systemic spread or tumor direct extension. In patients with cardiac masses, it is mandatory to accurately define their malignant potential, the exact anatomic location, and the response to treatment in order to optimize therapeutic strategy. In the past few years, cardiac magnetic resonance imaging (CMR) and multitracer positron emission tomography (PET)/computed tomography have revolutionized the noninvasive diagnosis of cardiac tumors, allowing precise morphological and functional disease characterization. Nowadays, coregistered imaging from PET/computed tomography (CT) devices or combined from separately acquired CMR and PET images, represents a great technological development able to influence clinical decisions.

Here, we didactically present PET, CMR, and fused PET/CMR images highlighting the strengths of such combined morpho-functional investigation in 5 selected patients with cardiac malignancies and addressed for tumor aggressiveness evaluation (Figure 1), lesion topographic assessment (Figure 2), disease extension definition (Figures 3 and 4), or treatment efficacy evaluation (Figure 5).
An 83-year-old man with previous history of clear cell renal cell carcinoma presented with chest pain and acute heart failure. Transthoracic echocardiography revealed a right ventricle mass. Cardiac magnetic resonance (CMR) imaging demonstrated a voluminous intracavitary tissular mass (arrows) originating from right ventricle wall and infiltrating the pericardium. (A) Lesion showed intermediate signal intensity on dark blood images, (B) diffuse hyperintensity on T2-weighted fat-saturated dark-blood images, (C) and heterogeneous enhancement on delayed post-contrast inversion recovery sequences. (D) Positron emission tomography (PET), (E) and PET and CMR hybrid images (arrow) revealed intense $^{18}$F-fluorodeoxyglucose uptake on cardiac lesion (maximum standardized uptake value: 14.1), suggesting a malignant origin. (F) Pathologic diagnosis of clear cell renal cell carcinoma was reached after pericardial biopsy (hematoxylin and eosin ×200, cytokeratin [AE1/AE3] positive ×400). This case highlights the central role of PET/CMR in the non-invasive diagnosis of cardiac malignancies.
FIGURE 2 Definition of Cardiac Tumoral Extension: Locally Infiltrating Right Ventricle Metastasis From Vulvar Carcinoma

An 82-year-old woman with history of vulvar carcinoma underwent follow-up 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT). (A,B) Large area of intense and heterogeneous glucose metabolism (maximum standardized uptake value: 10.2) involving the right ventricle wall was revealed on PET/CT images (arrow). A metastatic cardiac involvement was suggested. Cardiac magnetic resonance imaging (CMR) confirmed tumoral right ventricle involvement with pericardial invasion. (C) A 38 × 24 mm infiltrating mass of right ventricle wall with mobile intracavitary component and intermediate signal intensity was distinguished on dark-blood images. (D) Cardiac lesion was characterized by heterogeneous hyperintensity on T2-weighted fat-saturated dark-blood images, (E) and heterogeneous contrast enhancement with central hypointense area. (F) Tumor heterogeneity was clearly showed on PET and CMR hybrid images. This case highlights the interest of PET/CMR for the assessment of cardiac tumor local extension.
A 69-year-old man with stage IV melanoma treated by surgery, chemotherapy, and immunotherapy presented with a right atrium asymptomatic mass revealed on echocardiography. (A) Cardiac magnetic resonance imaging (CMR) confirmed the presence of atrial lesion (arrows) with intermediate signal intensity on T1-weighted dark-blood, (B) T2-weighted fat-saturated dark-blood images, and (C) steady-state free precession sequences. Minimal pericardial effusion was also showed. (D) T1- and T2-mapping images revealed a short T1 (600 ms vs. 1030 ms in normal myocardium), (E) and moderately increased T2 (60 ms vs. 50 ms in normal myocardium). (F) Atrial lesion presented moderate and heterogeneous gadolinium enhancement and intense fluorodeoxyglucose uptake (standardized uptake value: 9.3) (G) on positron emission tomography/computed tomography (PET/CT), and (H) PET and CMR hybrid images. This case highlights the potential interest of combined morpho-functional quantitative parameters as native T1- and T2-mapping values and maximum standardized uptake value for tumors characterization, which is particularly useful for melanoma metastases.
A 52-year-old woman assessed for primary staging of metastatic neuroendocrine tumor (NET) of unknown origin. Transthoracic echocardiography was normal. (A,D,G) Intense focal uptake (maximum standardized uptake value: 7.3) of 6-L-18F-fluorodihydroxyphenylalanine (18F-FDOPA) was showed on positron emission tomography/computed tomography (PET/CT) in the upper wall of left atrial appendage, without abnormalities on coupled CT scan. NET metastasis was suggested (arrows) and patient underwent cardiac magnetic resonance imaging (CMR). (B,E,H) A few millimeters nodule imbedded in upper wall of the left atrium was detected on steady-state free precession sequence showing minimal peripheral enhancement on post-contrast acquisition. (C,F,I) The left atrial nodule was precisely and easily recognized on PET and CMR hybrid images. This case suggests that PET/MR with radiotracers specifically targeting neuroendocrine phenotype (i.e., 18F-FDOPA, 68Ga-DOTA-peptides) will increase the noninvasive detection of asymptomatic cardiac metastases in patients with NETs.
A 46-year-old man presented with chest pain and voluminous right upper thoracic mass. Staging echocardiography was normal. Lesion biopsy revealed diffuse large B-cell lymphoma. (A) Pretreatment positron emission tomography/computed tomography (PET/CT) also showed intense (maximum standardized uptake value: 12.3), pathologic, and multifocal right atrial 18F-fluorodeoxyglucose (18F-FDG) uptake suggesting cardiac lymphoma extension. (B) Cardiac magnetic resonance imaging (CMR) confirmed diffuse tissular infiltration of right atrium walls (arrows), minimal pericardial effusion, without adjacent structures invasion on steady-state free precession sequence. (C) On post-contrast inversion, recovery images atrial tumor presented with homogenous hyposignal compared with normal myocardium. (D) PET and CMR hybrid images well showed the hypermetabolic atrial tumor infiltration. (E) 18F-FDG PET/CT, (F, G) CMR, and (H) fused PET and CMR early performed after chemotherapy showed complete morpho-functional regression of atrial tumor (dotted arrows). This case highlights the role of PET/CMR in the evaluation of treatment efficacy.
The prevalence of obesity has dramatically increased. Obesity represents a risk factor for coronary artery disease (CAD) and mortality (1). The identification of CAD is a major challenge in morbidly obese patients. The capacity for exercise is often limited, leading to inconclusive stress test results. Stress echocardiography may suffer from poor echogenicity, and single-photon emission computed tomography can be limited by attenuation, with a higher incidence of false-positive results. Coronary computed tomographic angiography is hampered by patient morphology and higher radiation. The accuracy of stress perfusion cardiovascular magnetic resonance (CMR) is not established for risk stratification in morbidly obese patients (body mass index $\geq 40$ kg/m$^2$).

A total of 444 morbidly obese patients with suspected CAD (55% women, mean age 59 ± 11 years, mean body mass index $44.8 \pm 18.0$ kg/m$^2$ [range 40 to 66 kg/m$^2$]) were prospectively referred for stress perfusion CMR (chest pain [22%], dyspnea [28%], high cardiovascular risk [63%], inconclusive functional test results [14%]) using a large-bore Siemens Magneton Aera 1.5-T scanner with 48-channel coils. After standard cine, hyperemia was induced with dipyridamole (0.84 mg/kg for 3 min). Then, a bolus of 0.1 mmol/kg gadolinium chelates (Dotarem, Guerbet, Villepinte, France) was injected (5 ml/s) with acquisitions of 4 to 6 left ventricular short-axis and 2 long-axis views using the first-pass perfusion technique. After 10 min, cross-registered inversion recovery gradient-echo sequences were acquired to detect late gadolinium enhancement (LGE). The analysis of perfusion images was done visually by 2 blinded experienced observers (17-segment model). The definition of inducible ischemia was based on accepted criteria.

The follow-up consisted of yearly clinical visits and additional contacts in case of events. The primary clinical endpoint was the occurrence of \(\geq 1\) of the combined major adverse clinical event(s) (MACE) (cardiac death or aborted sudden cardiac death, nonfatal myocardial infarction, sustained documented ventricular tachycardia, hospitalization for heart failure [New York Heart Association functional class III or IV], ischemic stroke, and coronary revascularization \(\geq 90\) days after stress CMR). Clinical event adjudication was reached by consensus between 2 senior cardiologists. Patients who underwent coronary revascularization \(\leq 90\) days after index CMR were censored. Cumulative incidence rates of individual and composite outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards methods were used to identify the predictors of MACE.

There were no major cardiovascular adverse events during or shortly after CMR, only minor events that resolved rapidly with 250 mg aminophylline and/or adequate treatment. Among 444 included patients, 404 (91%) completed clinical follow-up (median 5 years; range 3.5 to 6.8 years). Overall, there were 72 MACE: 19 deaths (6 cardiovascular), 16 hospitalizations for heart failure, 19 coronary revascularizations (3 bypass surgery), 6 strokes, 6 nonfatal myocardial infarctions, and 3 episodes of sustained documented ventricular tachycardia. In univariate analysis, variables associated with the occurrence of MACE were the presence of LGE (odds ratio [OR]: 11.78; 95% confidence interval [CI]: 4.81 to 28.85; \(p < 0.0001\)), inducible myocardial ischemia (OR: 13.76; 95% CI: 5.69 to 33.23; \(p < 0.0001\)), left ventricular ejection fraction (\(p < 0.01\)), and hypertension (\(p = 0.03\)). The presence of LGE (OR: 6.80; 95% CI: 1.25 to 37.05; \(p = 0.01\)) and inducible myocardial ischemia (OR: 6.20; 95% CI: 1.14 to 33.63; \(p = 0.02\)) were the only 2 variables associated with cardiovascular mortality. Patients without inducible ischemia or LGE experienced a lower rate of MACE than those with inducible ischemia (3.3% vs. 12.4%; \(p < 0.001\)) (Figure 1A). In multivariate analysis, the presence of inducible ischemia was independently associated with MACE (hazard ratio [HR]: 5.05; 95% CI: 1.37 to 9.29; \(p < 0.0001\)) and cardiovascular mortality (HR: 8.84; 95% CI: 1.58 to 50.00; \(p = 0.013\)); the same association was observed for the presence of LGE (HR: 3.60; 95% CI: 1.87 to 6.90; \(p < 0.0001\); and HR: 5.32; 95% CI: 1.53 to 47.62; \(p = 0.015\), respectively). Using Kaplan-Meier analysis, patients with inducible ischemia had significantly lower event-free survival for MACE and cardiovascular mortality compared with patients without ischemia (\(p < 0.0001\)) (Figure 1B). This finding held true in men and women, without sex differences. By Cox proportional hazards modeling, the addition of inducible ischemia to a model
including LGE and left ventricular ejection fraction resulted in significant incremental prognostic value for MACE (p < 0.0001). In patients presenting with ischemic symptoms and negative findings on stress CMR, the event-free rate by year of follow-up was 98.9%, 95.9%, 92.9%, 92.3%, and 89.2%, respectively.

This was a single-center study but with a high volume of procedures (>3,700 stress CMR examinations per year). For the 40 patients lost to follow-up, the National Registry of Death was reviewed, which strengthens the data on mortality. Overall, 46 MACE occurred in patients with negative results on stress CMR, underlying the relatively low sensitivity of this test for the prediction of subsequent events.

In conclusion, stress perfusion CMR is feasible and safe and has accurate discriminative prognostic value in morbidly obese patients.

Marine Kinnel, MD
Jérôme Garot, MD, PhD*
Théo Pezel, MD
Thomas Hovasse, MD
Thierry Unterseeh, MD

Stéphane Champagne, MD
Yves Louvard, MD
Marie Claude Morice, MD
Philippe Garot, MD
Francesca Sanguineti, MD

*ICPS - CMR Department
Hôpital Privé Jacques Cartier
Ramsay-Générale de Santé
6 Avenue du Noyer Lambert
91300 Massy
France

E-mail: jgarot@angio-icps.com

REFERENCE
1. Romero-Corral A, Montori VM, Somers VK, et al. Association of body-weight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666-78.
Myocardial Inflammation and Edema in People Living With Human Immunodeficiency Virus

The burden of cardiovascular disease in people living with HIV (PLWH) has tripled over the last 20 years, with cardiac manifestations of disease ranging from coronary disease to heart failure (1). The pathophysiological mechanisms involved in the development of HIV cardiomyopathy remain elusive. Subclinical structural and functional changes have been demonstrated in PLWH, but studies that used advanced imaging techniques focused on patients already treated with antiretroviral therapy (ART), potentially limiting the understanding of cardiac manifestations of HIV.

In this study, we evaluated myocardial changes in both treated and untreated PLWH by implementing advanced cardiac magnetic resonance (CMR) with tissue characterization by parametric mapping techniques in the upper- to middle-income country of Peru. Study participants were prospectively recruited, and each provided written informed consent. The study group consisted of 51 PLWH; 26 were on ART and 25 patients were treatment-naïve. Twenty-one healthy control subjects were selected by frequency matching. No patient had hepatitis C co-infection. Treatment-naïve patients were defined as newly diagnosed patients with HIV, with CMR performed either before or within 14 days of initiating ART. Of the ART-treated group, 22 (85%) received both nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. The average time since the initial diagnosis of HIV was 5.0 ± 4.4 years. Undetectable viral load was defined as <40 copies/ml. All scans were performed with a 3-T MRI scanner (Magnetom, Prisma, Siemens, Siemens Medical Solutions, Erlangen, Germany). The protocol included cine imaging for volume and function assessment (strain analysis with feature tracking), as well as Modified Look-Locker Inversion Recovery T1 and T2 mapping. Gadodate meglumine (0.1 mmol/kg) was administered for late gadolinium enhancement (LGE) imaging, and the extracellular volume (ECV) fraction was also calculated. CMR readers were blinded to patients’ categories.

There were no significant differences in baseline characteristics and cardiac risk factors between patients and control subjects. Compared with control subjects, PLWH had reduced left ventricular (LV) function (LV ejection fraction [LVEF]: 61.4 ± 4.1% vs. 64.7 ± 2.4%; p = 0.001) and global longitudinal strain (−17.6 ± 3.3% vs. −21.0 ± 3.8%; p = 0.002). PLWH had increased native T1 (1,294 ± 20 ms vs. 1,230 ± 9 ms; p < 0.001), T2 (41.5 ± 2.4 ms vs. 36.4 ± 1.4 ms; p < 0.001), and global ECV (28.5 ± 1.5% vs. 24.8 ± 0.9%; p < 0.001). Among PLWH, 39% had LGE versus none of the control subjects (p < 0.001), with the area of LGE being mid or subepicardial in the septal and inferolateral walls. Nontrivial pericardial effusions (≥5 mm) were more common among PLWH compared with control subjects (29% vs. 5%; p = 0.004) (Figure 1A).

Untreated PLWH had higher global native T1 (1,304 ± 20 ms vs. 1,285 ± 16 ms; p < 0.001) and ECV (29.3 ± 0.7% vs. 27.7 ± 1.3%; p < 0.001) compared with those on ART (Figure 1B). For PLWH, higher ECV was associated with a lower CD4 count, which was independent of age, sex, and LVEF (r = −0.46; p = 0.001). Similarly, patients with a detectable viral load had higher ECV (29 ± 1.1 vs. 27.5 ± 1.3; p < 0.001) and higher native T1 (1,300 ± 21.2 vs. 1,286 ± 16.8; p = 0.02) than patients with an undetectable viral load (Figure 1C).

Consistent with previous studies (2,3), these data support a high prevalence of subclinical myocardial dysfunction and structural changes in PLWH. However, this was the first study that detected a significant expansion in ECV in PLWH, which suggested a greater myocardial impact of HIV than previously recognized, even in a young patient cohort (mean age: 36 years). The elevation in T1 and T2 mapping values seen in PLWH was consistent with previous studies that proposed myocardial inflammation as a component of the pathophysiological mechanism of HIV cardiomyopathy (4). Furthermore, these structural changes were more prominent in untreated patients (higher native T1 and ECV) compared with patients on ART, and ECV was higher in PLWH with lower CD4 counts and higher viral loads. These findings supported the notion that ART treatment likely had a protective myocardial effect. The presence of cardiac structural changes in PLWH, particularly the degree of ECV expansion, raises several questions with regard to the optimal management of these patients, suggesting the need of prospective studies with serial cardiac evaluation.

ACKNOWLEDGMENTS The authors sincerely thank Dr. Raul Marquina, head of the Advanced Imaging Diagnostic Center at the International Clinic, Lima, Peru, for all the support and approval of the present study. The authors also thank radiographers Darwin Gonzales Zelada and Jonathan Infante, and Nurse Ana Graña at Cayetano Heredia Hospital.
Cardiac magnetic resonance (CMR) in (a) people living with HIV (PLWH) and (b) control subjects showing increased native T1 mapping and extracellular volume (ECV) in (c) PLWH. (B) Basal antero-septal mid-wall and infero-lateral subepicardial LGE in PLWH. (B) Antiretroviral (ART)-naive PLWH have elevated native T1 and ECV compared with those on ART. (C) Inverse correlation between (a) ECV with CD4 total count, and (b and c) patients with a detectable viral load >40 copies/ml have higher global ECV and global native T1.
exposure may be associated with numerous side effects. Although cardiac 18-fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in tailoring corticosteroid therapy, the effect of corticosteroid dose and duration on FDG-PET abnormalities is not known (2).

We studied patients with CS undergoing cardiac FDG-PET before and after corticosteroid therapy with prednisone. Our aim was to assess the effect of low (<40 mg/day) versus high (≥40 mg/day) burst dose (BD) prednisone and short (<40 days) versus long (≥40 days) duration of BD on abnormal FDG uptake. BD was defined as the maximum prednisone dose administered within 2 months of the initial PET. Duration of therapy (DT) was defined as the time from BD initiation until the dose was decreased by ≥10 mg/day for ≥4 days. Myocardial FDG uptake was assessed as the maximum standardized uptake value (SUVmax) and the number of involved segments (NIS) based on the standard 17-segment model. A significant reduction in FDG uptake was defined as a ≥25% decrease in NIS or SUVmax, as previously described (3).

Thirty-two patients with CS were included (median age 54 years, 31% women, 34% black). Seventeen met Heart Rhythm Society criteria for probable or definite CS (1), while 15 were diagnosed based on clinical findings and advanced cardiac imaging. Eight patients presented with ventricular arrhythmias, 2 with atrial arrhythmias, 12 with heart block, 6 with heart failure, and 4 with extracardiac disease. Extracardiac involvement was present in 26 patients and included the lung in 20, spleen in 7, liver in 6, skin in 5, eyes in 2, brain in 1, and bone in 1. All patients demonstrated abnormal FDG uptake on the initial cardiac PET, and 23 showed perfusion defects and 19 showed colocalization of perfusion abnormalities with FDG. Eighteen patients underwent cardiac magnetic resonance imaging, of which 15 demonstrated late gadolinium enhancement. Median BD was 40 (interquartile range [IQR]: 40 to 60) mg/day and DT was 33 (IQR: 28 to 67) days.

Median duration between initial and subsequent PET was 5 (IQR: 4 to 19) months. There was a significant decrease in myocardial FDG uptake (NIS: 7.6 ± 3.3 to 3.5 ± 4.7; p < 0.0001; SUVmax: 6.3 ± 3.7 to 2.1 ± 2.3; p < 0.0001). Twenty-six (81%) patients demonstrated a decrease in NIS, 5 (16%) an increase, and 3 (9%) no change. Twenty-eight (88%) patients demonstrated a decrease in myocardial SUVmax and 4 (12%) demonstrated an increase. Twenty-three (72%) patients demonstrated a ≥25% decrease in NIS of which 18 showed complete resolution. Twenty-six (81%) patients showed a ≥25% decrease in myocardial SUVmax, of which 14 showed complete resolution.
By linear regression analysis, there was no association between BD and percent change in NIS (ΔNIS) ($r^2 = 0.005; p = 0.70$) or percent change in myocardial SUVmax (ΔSUVmax) ($r^2 = 0.0008; p = 0.90$). Furthermore, there was no association between DT and ΔNIS ($r^2 = 0.01; p = 0.50$) or ΔSUVmax ($r^2 = 0.004; p = 0.70$).

Comparing patients with a ≥25% decrease in NIS (n = 23) with those without a ≥25% decrease in NIS (n = 9), there was no difference in BD (median 40 mg vs. 40 mg; p = 0.77) or DT (median 30 days vs. 50 days; p = 0.15). Comparing patients with a ≥25% decrease in SUVmax (n = 26) with those without a ≥25% decrease in SUVmax (n = 6), there was no difference in BD (median 40 mg vs. 40 mg; p = 0.43) or DT (median 30 days vs. 57 days; p = 0.23). Comparing patients with BD <40 mg/day (n = 7) versus ≥40 mg/day (n = 25), there was no difference in ΔNIS ($-52 \pm 61\% \text{ vs. } -49 \pm 90\%; p = 0.9$) or ΔSUVmax ($-71 \pm 37\% \text{ vs. } -56 \pm 62\%; p = 0.50$) (Figure 1). Finally, comparing patients with DT <40 days (n = 18) versus ≥40 days (n = 14), there was no difference in ΔNIS ($-67 \pm 45\% \text{ vs. } -26 \pm 112\%; p = 0.20$) or ΔSUVmax ($-67 \pm 47\% \text{ vs. } -50 \pm 70\%; p = 0.40$).

This study had several important limitations. First, it is not known whether a ≥25% decrease in NIS or SUVmax represents a clinically significant improvement. Second, doses of prednisone <40 mg/day are lower than the BDs used at other institutions. Third, because of the small number of patients included, it is possible that a difference in PET responsiveness between patients treated with low versus high BD prednisone, or short versus long duration of burst prednisone, exists, but was not detected in our analysis.

In conclusion, corticosteroid therapy is associated with significant decreases in abnormal myocardial FDG uptake on serial PET examinations in approximately 3 in 4 patients with CS. However, there does not appear to be a significant difference in FDG-PET responsiveness between patients with CS treated with a low versus high dose, nor a short versus long duration, of prednisone therapy.

David R. Okada, MD
Elie Saad, MD
Alison L. Wand, MD
Jan M. Griffin, MBBC
Edward K. Kasper, MD
Edward H. Chen, MD
Jonathan Chrispin, MD
Harikrishna Tandri, MD
Liija B. Solnes, MD, MBA
Nisha A. Gilotra, MD*

*Division of Cardiology
Johns Hopkins Hospital
600 North Wolfe Street
Baltimore, Maryland 21287
E-mail: naggarw2@jhmi.edu

https://doi.org/10.1016/j.jcmg.2019.12.013
Letters to the Editor

Left Ventricular Intramyocardial Fat
Detected on Cardiac Computed Tomography in Patients With Stable Chest Pain

Histopathologic studies described subendocardial or transmural intramyocardial fat (IMF) at the site of prior myocardial infarction (MI) (1). In patients with stable chest pain with no history of MI, myocardial scar phenotypic for MI depicted with late gadolinium enhancement is identified in 11% to 25% (2). State-of-the-art computed tomography (CT) with submillimeter spatial resolution permits good visualization of focal adipose tissue in the left ventricle (LV). In patients with known prior MI, focal subendocardial or transmural LV-IMF depicted by cardiac CT, has been demonstrated to represent fatty reparation of the MI (3). We aimed to determine the prevalence and association of LV-IMF with cardiovascular (CV) risk and underlying coronary artery disease (CAD) in patients with suspected stable CAD with no history of MI.

We included patients from the PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) trial randomized to coronary CT and received noncontrast and contrast-enhanced cardiac CT (CT angiography [CTA]). We analyzed CT images for presence of LV-IMF blinded for patient data and the core lab reported CAD findings using an open source PACS-DICOM viewer (RadiAnt [Medixant, Poznań, Poland]). LV-IMF was defined as focal low attenuation (~30 Hounsfield units) with subendocardial or transmural appearance in the LV. Cases were excluded with LV-IMF with midmyocardial or subepicardial appearance. Noncontrast CT images were used to define the presence of LV-IMF and CTA images were used to specify the extent and location based on the 17-segment myocardial model (4). The LV-IMF-supplying artery was defined based on American Society of Echocardiography criteria (4) and visual assessment of coronary anatomy (dominance and side branches) on coronary CTA datasets (Figure 1). We compared CV risk and CAD extent between patients with and without LV-IMF. We further determined the extent and severity of coronary artery calcium (CAC) and CAD in IMF-supplying artery versus nonsupplying arteries using a multivariate multilevel mixed-effects model, adjusting for age, sex, body mass index, and ASCVD (Atherosclerotic Cardiovascular Disease) risk score. Finally, we compared the rate of major adverse CV events (CV death, MI, or hospitalization for unstable angina) between patients with and without LV-IMF.

We evaluated 3,705 patients (48.9% men; 60.4 ± 8.2 years of age) and observed LV-IMF in 5.4% (n = 200 of 3,705). In 75% (n = 150 of 200), LV-IMF affected <3 myocardial segments. Patients with LV-IMF were slightly older (60.3 ± 8.2 years of age vs. 63.9 ± 8.6 years of age; p < 0.001), had modestly elevated ASCVD risk (ASCVD risk score ≥7.5; 74.2% vs. 66.7%; p = 0.006), and had higher prevalence and extent of CAD (CAC >0: 77.0% vs. 63.5%; p < 0.001; CAC >400: 22.5% vs. 12.5%; p < 0.001; any CAD: 79.5% vs. 65.5%; p < 0.001), and were independently associated with LV-IMF (for any CAC, odds ratio [OR]: 1.65; 95% confidence interval [CI]: 1.15 to 2.37; p = 0.007; for CAC >400, OR: 1.28; 95% CI: 0.93 to 1.77; p = 0.004; and for any CAD, OR: 1.78; 95% CI: 1.22 to 2.59; p = 0.003).

The IMF-supplying artery was the left main artery in 2% (n = 4 of 200), the left anterior descending artery in 77% (n = 146 of 200), the right coronary artery in 19% (n = 38 of 200), and the left circumflex artery in 4% (n = 8 of 200). CAD in IMF-supplying arteries was significantly more severe compared with in nonsupplying arteries (CAC >400: 9.7% [n = 19 of 196] vs. 3.6% [n = 14 of 391]; CAC >50%: 12.3% [n = 24 of 196] vs. 6.2% [n = 24 of 391]; high-risk plaque: 13.3% [n = 26 of 196] vs. 6.7% [n = 26 of 391]), independently of CV risk (for CAC >400, OR: 3.13; 95% CI: 1.49 to 6.55; p = 0.003; for obstructive CAD, OR: 2.40; 95% CI: 1.30 to 4.45; p = 0.005; for high-risk plaque, OR: 2.27; 95% CI: 1.25 to 4.10; p = 0.007).

The overall rate of major adverse CV events was 2.4% (n = 88 of 3,705), and did not differ between those with and those without IMF in (2.5% [n = 83 of 3,505] vs. 2.4% [n = 5 of 200]; p = 0.914).

© 2020 by the American College of Cardiology Foundation. Published by Elsevier.

Please note: Dr. Tandri has served as a consultant for Abbott and St. Jude Medical. Dr. Solnes has served as a consultant for Projenics Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

REFERENCES

1. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014;11:1305-23.
2. Chareonthaitawee P, Beanlands RS, Chen W, et al. Joint SNMMI-ASNC expert consensus document on the role of (18)F-FDG PET/CT in cardiac sarcoidosis. J Nucl Cardiol 2017;24:1741-58.
3. Lee PI, Cheng G, Alavi A. The role of serial FDG PET for assessing therapeutic response in patients with cardiac sarcoidosis. J Nucl Cardiol 2017;24:19-28.
In a large prospective multicenter study of patients with suspected CAD with no history of MI, the prevalence of subendocardial or transmural LV-IMF is about 5%, mostly limited to 1 to 2 myocardial segments. The IMF-supplying artery had significantly more CAD compared with nonsupplying arteries in the same patient, independent of CV risk. Overall, in patients with LV-IMF with typical phenotypic appearance for MI, there is a possibility that LV-IMF might be the sign of clinically silent MI.

Júlia Karády, MD*
Thomas Mayrhofer, PhD
Borek Foldyna, MD
Alexander Ivanov, BS
Yasuka Kikuchi, MD
Maros Ferencik, MD, PhD, MCR
Michael T. Lu, MD, MPH
Stefan B. Puchner, MD
Hamed Emami, MD
Nandini M. Meyersohn, MD
Daniel O. Bittner, MD
Pál Maurovich-Horvat, MD, PhD
Pamela S. Douglas, MD
Udo Hoffmann, MD, MPH
*Cardiovascular Imaging Research Center
Massachusetts General Hospital-Harvard Medical School
165 Cambridge Street, Suite 400
Boston, Massachusetts 02114
E-mail: jkarady@mgh.harvard.edu

Cardiac computed tomography (CT) image analysis to detect of left ventricular intramyocardial fat (LV-IMF) (1) and definition of the IMF–supplying versus nonsupplying vessels (2 and 3). The arrowheads are indicating a focal low attenuation (below -30 Hounsfield units) with subendocardial appearance in the left ventricle as detected on the noncontrast and contrast enhanced CT images. CAC = coronary artery calcification; LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

FIGURE 1  Cardiac CT Image Analysis

1 Non-contrast and contrast enhanced CT image analysis
2 Localization of IMF based on the 17 segment myocardial model
3 Definition of the culprit vessel

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.
A retrospective magnetic resonance imaging (MRI) study on a large cohort of children with thalassemia major (TM) showed cardiac involvement by early childhood; 21% of children presented with abnormal cardiac T2* and 16% with cardiac fibrosis. Moreover, moderate and/or severe liver iron overload (IO) was found in the 68% of the children (1). These findings provided the basis for the first prospective MRI study on children with TM aimed to evaluate changes in IO parameters and biventricular function, as well as development of cardiac fibrosis in a clinical practice setting.

We studied 68 pediatric patients with TM (36 females; age 13.7 ± 3.1 years) enrolled in the MIOT (Myocardial Iron Overload in Thalassemia) Network who performed a follow-up study at 18 ± 3 months. All MRIs were performed without sedation. The study complied with the Declaration of Helsinki.

IO was quantified by the T2* technique. A multislice approach was adopted for the heart and 4 patterns of myocardial IO (MIO) were identified (2). Liver T2* was converted into liver iron concentration (LIC). Biventricular function was quantified by cine images. Myocardial fibrosis was detected by the late gadolinium enhancement technique (3,4).

All patients were under transfusion and chelation, which started at a mean age of 1.6 ± 0.8 years and 2.9 ± 1.1 years, respectively. At the baseline MRI, 18 (27.5%) patients were treated with deferoxamine, 7 (10.3%) with deferiprone, 37 (54.4%) with deferasirox, and 6 (8.8%) with combination of deferoxamine+deferiprone. After the first MRI, the chelation regimen was changed in 25 (36.8%) patients; they were switched to a different chelator or underwent dose modification.

At follow-up, we detected a significant increase in global heart T2* values (29.7 ± 11.2 ms vs. 31.4 ± 10.3 ms; p = 0.031), a significant reduction in the number of segments with T2* <20 ms (4.4 ± 6.1 vs. 3.5 ± 5.4; p = 0.046), and a significant reduction in MRI LIC values (10.8 ± 9.5 mg/g dry weight (dw) vs. 9.3 ± 9.1 mg/g dw; p = 0.009).

Percentage changes in global heart T2*/month were not associated with initial, final, or percentage changes in MRI LIC values.

At baseline, a mid-septum T2* <20 ms was observed in 17 (25.0%) patients, but 43 (63.2%) patients showed MIO (at least 1 segmental T2* <20 ms), which confirmed the segmental approach more sensitive and particularly useful in the pediatric population (1). In the 43 patients with baseline MIO, the following changes were detected at the follow-up: improvement (transition to a better risk class on the basis of the MIO patterns from worst to normal) in 17 (39.5%) patients; stabilization (no change in the risk class) in 24 (55.8%) patients; and worsening (transition to a worse risk class) in 2 (4.7%) patients (Figure 1). Of the 17 patients who improved, only 2 had no hepatic IO (LIC >3 mg/g dw). Among the 25 patients with no MIO, 9 (36.0%) worsened, developing MIO at follow-up. The high rate of worsening could be explained by a more conservative approach to chelation therapy (lower mean dose of chelator and delayed dose increase) in comparison to adult patients (5).

We detected positive cardiac remodeling with a significant reduction in the biventricular end-diastolic volume indexes (left: 93.9 ± 19.3 ml/m² vs. 91.1 ± 21.1 ml/m²; p = 0.027; right: 88.9 ± 19.7 ml/m² vs. 82.2 ± 18.3 ml/m²; p = 0.003), although these parameters tended to increase with age (6). This finding probably reflected the good rates of blood transfusions and the reduction of MIO detected in our population.

For the first time, we longitudinally studied macroscopic myocardial fibrosis, a significant prognosticator in adult patients (4), in a pediatric population with TM (N = 40) who received gadolinium at both scans. Six (15.0%) patients had myocardial fibrosis at baseline, and fibrosis was detected in all of them at follow-up, with a comparable extent (0.8 ± 0.4% vs. 0.8 ± 0.5% of the myocardial mass; p = 0.686). At follow-up, 4 new occurrences were detected. Therefore, myocardial fibrosis was not
progressive but not reversible at a mid-term follow-up. This study confirmed the correlation between fibrosis and MIO in pediatric patients. In a retrospective study, children with myocardial fibrosis showed significantly lower cardiac T2* (1), and in the present longitudinal cohort, all newly diagnosed patients at follow-up had baseline global heart T2* < 20 ms.

In conclusion, the consistent percentage of pediatric patients with MIO at baseline and the significant rate of development of IO at follow-up strongly recommends regular MRI monitoring for further improvement of iron burden in pediatric patients using a prompt and tailored chelation regimen.
Feasibility of Computed Tomography Perfusion for Detection of Cardiac Allograft Rejection Following Heart Transplantation

Cardiac allograft rejection (CAR) is one of the most common complications in the first year after orthotopic heart transplantation (OHT) (1). Accurate and timely diagnosis of CAR is crucial, especially because effective immunosuppressive therapies are available. Repeated endomyocardial biopsy (EMB) is the gold standard for the diagnosis of CAR, but it requires radioscopy and is associated with 0.2% to 5.5% of serious complications (2,3). Therefore, we explored less invasive diagnostic strategies.

Dynamic computed tomography perfusion (CTP) is a novel noninvasive imaging method; however, its role in patients who have undergone OHT is unknown. Therefore, we aimed to determine the feasibility of dynamic CTP as a noninvasive imaging method for identification of CAR, as evaluated histologically.

Consecutive patients were recruited before third week and the end of third month after OHT between March 2018 and May 2019. Study exclusion criteria were hemodynamically unstable condition, estimated glomerular filtration rate <45 ml/min/1.73 m², and contraindications to CTP, to iodine contrast, or to regadenoson. Twenty nontransplant patients with excluded significant coronary stenosis were used as a control group. The study received approval from the Ethics Committee. EMBs were obtained at 2, 3, 4, 6 to 8, and 12 weeks after OHT. The International Society for Heart and Lung Transplantation cardiac biopsy grades (0R/1R/2R/3R) were used (4).

All patients underwent stress dynamic CTP (Somatom Force, Siemens, Germany). For the CTP, 0.4 mg of regadenoson in a 5- to 10-s bolus and 35 ml of ioheksol (350 mgI/ml) with 5 ml/s flow rate were used. A tube voltage of 70 kV and automatic tube current up to 400 mA were used. A tube voltage of 70 kV and automatic tube current up to 400 mA were used. Anonymized CTP data were analyzed by an experienced reader (>10 years with cardiac computed tomography) blinded to patients’ clinical data. Semi-automatic analyses were performed using dedicated software (CT Myocardial Perfusion, Siemens). The presence of hypoperfused areas and measurements of myocardial blood flow (MBF) and myocardial blood volume (MBV) were obtained from regions of >0.5 cm² for basal, midventricular, and apical segments.

REFERENCES

1. Casale M, Meloni A, Filosa A, et al. Multiparametric cardiac magnetic resonance survey in children with thalassemia major: a multicenter study. Circ Cardiovasc Imaging 2015;8:e003230.
2. Meloni A, Restaino G, Borsellino Z, et al. Different patterns of myocardial iron distribution by whole-heart T2* magnetic resonance as risk markers for heart complications in thalassemia major. Int J Cardiol 2014;177:1012–9.
3. Pepe A, Positano V, Capra M, et al. Myocardial scarring by delayed enhancement cardiovascular magnetic resonance in thalassemia major. Heart 2009;95:1688–93.
4. Pepe A, Meloni A, Rossi G, et al. Prediction of cardiac complications for thalassemia major in the widespread cardiac magnetic resonance era: a prospective multicentre study by a multi-parametric approach. Eur Heart J Cardiovasc Imaging 2018;19:299–309.
5. Taher A, Elalfy MG, Al Zir K, et al. Importance of optimal dosing ≥30 mg/kg/d during deferasirox treatment: 2.7-yr follow-up from the ESCALATOR study in patients with beta-thalassemia. Eur J Haematol 2011;87:355–65.
6. Meloni A, Detterich J, Berdoukas V, et al. Comparison of biventricular dimensions and function between pediatric sickle-cell disease and thalassemia major patients without cardiac iron. Am J Hematol 2013;88:213–8.
FIGURE 1 Results of the Dynamic CTP

(A to C) Schematic heart cross sections and (D to I) dynamic computed tomography perfusion (CTP) results, presenting the normal myocardium, midwall patchy pattern, and ischemia. (J) Myocardial blood flow (MBF) and (K) myocardial blood volume (MBV) in patients after orthotopic heart transplantation (OHT) with and without rejection compared with the control group.
From 44 screened patients who underwent OHT, 32 did not meet inclusion and/or exclusion criteria. The final study population consisted of 12 patients who underwent OHT (9 males; age: 44.7 ± 11.9 years, body mass index: 25.6 ± 4.4 kg/m²) and 20 control subjects (9 males; age: 64.4 ± 8 years; body mass index: 27.0 ± 3.2 kg/m²).

Of 46 biopsies, 31 were classified as group 0, 12 as group 1, 2 as group 2, and 1 was nondiagnostic. None of the patients had antibody-mediated rejection. Biopsies were matched with CTP in a 1-day interval (range 1.0 to 1.5 days). Three patients had active rejection, 5 patients had past rejection, and 4 had no rejection.

In dynamic CTP, 6 of 512 evaluated segments were nondiagnostic. Qualitatively, some dynamic CTP displayed diffuse, multisegmental, and irregular hypoperfused areas localized in the mid-wall myocardial layer, which we called midwall patchy pattern (MPP) (Figure 1). The receiver-operating characteristic analysis showed that presence of >1 segment with MPP was associated significantly with grade ≥1R with 100% sensitivity and 96% specificity (area under the curve: 0.974; p < 0.001). Moreover, the number of segments with MPP correlated significantly with number of grade ≥1R (p < 0.03) but was not related to the time from OHT (p = 0.69).

Quantitatively, in the OHT group, segments diagnosed with MPP compared with normal segments differed significantly for MBF (116.3 ml/100 ml/min; range 104.0 to 129.7 vs. 179.7 ml/100 ml/min; range 157.3 to 209.2) and MBV (13.2 ml/100 ml; range 11.3 to 144.2 mGy/cm). No severe adverse reactions to regadenoson or contrast agent were observed. 144.2 mGy/cm. No severe adverse reactions to regadenoson or contrast agent were observed.

The main findings of this study were: 1) in patients after OHT, CAR was related to the presence of hypoperfusion areas that demonstrated multisegmental MPP on dynamic CTP; 2) in patients with rejection, the MBF in segments without MPP did not differ compared with the control group; and 3) the extent of perfusion defects in patients after OHT increased with the number of rejection episodes.

Early CAR clinical manifestations may present late, and routine EMB is not only an aggressive, but also sometimes false negative examination for rejection detection. There is still a need for improvement of noninvasive diagnostics following OHT. Dynamic CTP advantages include safety, simplicity, and the ability for qualitative and quantitative analyses, but disadvantages include radiation and contrast use. To the best of our knowledge, this was the first study that analyzed dynamic CTP in heart transplantation recipients. The study findings might be limited by small sample size and low eligibility due to the highly restrictive inclusion criteria aimed to protect patients in the pilot study. However, high statistical significance of the revealed relationships might reinforce our findings and suggest diagnostic robustness of the novel method.

In conclusion, the dynamic CTP is sensitive to early perfusion abnormalities in heart transplantation recipients with CAR and has the potential to serve as an alternative screening tool. Our pilot study resulted in findings that need confirmation in a larger patient population with wider eligibility criteria.

Anna Oleksiak, MD, PhD‡ Małgorzata Sobieszczanka-Małek, MD, PhD‡ Mariusz Kruk, MD, PhD Tomasz Zielinski, MD, PhD Anna Drohomirecka, MD Krzysztof Komuda, MD Małgorzata Karczmarz, MD Mariusz Kusmierzycz, MD, PhD Jacek Kądziela, MD, PhD Marcin Demkow, MD, PhD Cezary Kępka, MD, PhD

*National Institute of Cardiology
Department of Intensive Cardiac Therapy
Alpejska 42
Warsaw 04-628
Poland
E-mail: aoleksiak@ikard.pl
https://doi.org/10.1016/j.jcmg.2020.01.004
© 2020 by the American College of Cardiology Foundation. Published by Elsevier.

Please note: Drs. Oleksiak and Sobieszczanka-Małek contributed equally to this work. This study was funded by the Institute of Cardiology (grant 2.3/V/18) and by the National Science Centre, Poland (grant 2015/19/B/N05/00300). The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors are grateful to Prof. Maciej Pronicki and the team at the Department of Pathology at the Children’s Memorial Health Institute in Warsaw for interpretation of the EMBs. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

REFERENCES

1. Raichlin E, Edwards BS, Kremers WK, et al. Acute cellular rejection and the subsequent development of allograft vasculopathy after cardiac transplantation. J Heart Lung Transplant 2009;28:320-7.
2. Holzmann M, Nicko A, Kühl U, et al. Complication rate of right ventricular endomyocardial biopsy via the femoral approach: a retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period. Circulation 2008;118:1722-8.
3. Saraiva F, Matos V, Gonçalves L, Antunes M, Providência LA. Complications of endomyocardial biopsy in heart transplant patients: a retrospective study of 2117 consecutive procedures. Transplant Proc 2011;43:1908-12.
Myocardial shortening after aortic valve closure, also known as post-systolic shortening (PSS), has been suggested as a marker of regional myocardial dysfunction. Despite PSS being commonly associated with myocardial ischemia (1), it may also occur in the setting of passive dyskinesia (2). Recent studies from our group have demonstrated how PSS assessed by speckle tracking echocardiography (STE) provides prognostic information in various populations, and, in particular, is associated with heart failure (HF) (3,4). The aim of this study was to assess if PSS by STE could predict adverse cardiovascular events in patients with type 2 diabetes mellitus (T2DM).

This was a secondary analysis of a prospective, observational, multicenter cohort study that originally included 1,030 participants with T2DM (Thousand & 2 Study) (5). We excluded patients with atrial fibrillation (n = 62), ischemic heart disease (n = 113), known HF (n = 21), interventricular conduction disturbances (n = 62), and ineligible images for STE (n = 29). A total of 743 patients (mean age: 63 ± 10 years; 62% men) were included.

The primary endpoint was major adverse cardiovascular event(s) (MACE), defined as a composite of myocardial infarction, HF, and cardiovascular death. The secondary endpoint was HF. We obtained information on cardiovascular outcomes from the Danish National Board of Health’s Patient Registry and the Danish Register of Causes of Deaths. Follow-up was 100%. It was not possible to differentiate between HF with preserved and reduced ejection fractions because these data were not available in Danish registries.

Using STE, we obtained peak systolic strain, post-systolic strain, and maximal strain from 1 cardiac cycle (Figure 1A). Global longitudinal strain (GLS) denoted the maximal strain, and the mean post-systolic index (PSI) was defined as: [(100 × (post-systolic strain – peak systolic strain))/maximal strain]. Measurements were averaged across 18 segments. Stress testing for ischemic changes was not performed.

In time to first-event analyses, we applied a single multivariable model of age, sex, hypertension, smoking status, duration of diabetes, dyslipidemia, estimated glomerular filtration ratio, use of insulin, glycosylated hemoglobin, systolic blood pressure, lipid ratio, left ventricular ejection fraction, left ventricular mass index, E/A ratio, left atrial volume index, and GLS. Prognostic performance was tested using Harrel’s C-statistics. Because of multiple comparisons, a p value <0.004 in the Cox models was considered significant, and in the other analyses, p values <0.05 were significant.

During a median follow-up of 4.5 years (interquartile range: 4.1 to 5.3 years), 93 (13%) patients experienced a MACE and 20 (3%) developed HF. In multivariable models, each 1% additional increase in average PSI was significantly associated with MACE (hazard ratio: 1.10; 95% confidence interval: 1.03 to 1.18; p = 0.003) and HF (hazard ratio: 1.25; 95% confidence interval: 1.10 to 1.41; p < 0.001) (Figure 1B). GLS modified the association (univariable: p = 0.003; multivariable: p = 0.049), such that the average PSI was a predictor of both endpoints in patients with GLS <15% (median cutoff for GLS; n = 372) but not in patients with GLS ≥15% (n = 371) (Figure 1B). When adding average PSI to the multivariable model in patients with GLS <15%, C-statistics increased significantly for HF (C-statistic: 0.81 vs. 0.85; p = 0.024) but not for MACE (C-statistic: 0.73 vs. 0.76; p = 0.24).

Patients with T2DM have an excess risk of cardiovascular disease and may benefit from timely and precise cardiovascular risk stratification. In this study, we demonstrated that PSS assessed by STE provided independent and prognostic information on adverse cardiovascular events in T2DM. In addition, the prognostic value of PSS was enhanced in patients with reduced GLS. Because PSI is a byproduct of GLS and is quickly obtained in a clinical setting, it could be reported on a routine basis in well-defined populations when performing STE. Future and larger clinical studies are required to confirm this.
FIGURE 1  Schematic Drawing of Post-Systolic Shortening and Forest Plot

(A) Schematic drawing of speckle tracking profile. The red segment displays post-systolic shortening. (B) Forest plot of the association between average post-systolic index (PSI) and cardiovascular events. GLS = global longitudinal strain; MACE = major adverse cardiovascular event(s).
Niels Andersens Vej 65
2900-Hellerup
Denmark
E-mail: denlilleflur@hotmail.com
https://doi.org/10.1016/j.jcmg.2020.01.003

© 2020 by the American College of Cardiology Foundation. Published by Elsevier.

Please note: Dr. Jensen has been a consultant on advisory boards or an invited speaker for AstraZeneca, Novo Nordisk, Novartis, and GE. Dr. Biering-Sørensen has been a member of the steering committee of the Aussen-financed GALACTIC-HF trial; has served on the advisory boards of Sanofi Pasteur and Aangen; and has received speaker honoraria from Aagnostos and Sanofi Pasteur. Dr. Vibbé has received consultancy fees and speaker honoraria from Aagnostos, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Novo Nordisk, Merck Sharp & Dohme, Sanofi, and Sun Pharma; and research grants were received from Novo Nordisk, Eli Lilly, and Boehringer. Dr. Rosing has received lecture fees from Novo Nordisk; has received consultancy fees and/or speaking fees (all fees to Steno Diabetes Center Copenhagen) from AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Eli Lilly, Merck Sharp & Dohme, Merck, Mundipharma, and Sanofi; has received research grants from AstraZeneca and Novo Nordisk; and holds shares in Novo Nordisk A/S. Dr. Jørgensen has received lecture fees from Novo Nordisk. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

REFERENCES

1. Voigt JU, Lindenmeier G, Exner B, et al. Incidence and characteristics of segmental postsystolic longitudinal shortening in normal, acutely ischemic, and scarred myocardium. J Am Soc Echocardiogr 2003;16:415-23.

2. Skulstad H, Edvardsen T, Urheim S, et al. Postsystolic shortening in ischemic myocardium: active contraction or passive recoil? Circulation 2002;106: 718-24.

3. Brainin P, Skaarup KG, Iversen AZ, et al. Post-systolic shortening predicts heart failure following acute coronary syndrome. Int J Cardiol 2019;276:191-7.

4. Brainin P, Haahr-Pedersen S, Sengelav M, et al. Presence of post-systolic shortening is an independent predictor of heart failure in patients following ST-segment elevation myocardial infarction. Int J Cardiovasc Imaging 2017;34:751-60.

5. Jørgensen PG, Jensen MT, Mogelvang R, et al. Impact of type 2 diabetes and duration of type 2 diabetes on cardiac structure and function. Int J Cardiol 2016;221:114-21.

Myocardial Evaluation of Post-Preeclamptic Women by CMR

Is Early Risk Stratification Possible?

Preeclampsia is a life-threatening disorder associated with long-term cardiovascular risk (1). We investigated cardiac alterations in post-preeclamptic women and control subjects using cardiovascular magnetic resonance (CMR) imaging. Diffuse injury of the myocardium was assessed by parametric mapping, focal injury was assessed by late gadolinium enhancement imaging, and cardiac function was evaluated by cine imaging and tissue tracking (strain). Exclusion criteria were CMR incompatibility (metal implants, kidney insufficiency [glomerular filtration rate <30 ml/min], claustrophobia, contrast medium allergy, current pregnancy or lactation, body weight >120 kg), pre-existent hypertension (>140/90 mm Hg) before index pregnancy, or previous diagnosis of cardiovascular disease. In total, 22 cases and 22 control subjects were enrolled. Participants were matched by age, body mass index (BMI), and parity. Control subjects did not receive any contrast agent; cases received 0.2 mmol/kg body weight of gadobutrol during the CMR procedure. The study (PPC1 [Post-Pregnancy Cardio Trial]; NCT03313063) was approved by the institutional review board of the Charité - Universitätsmedizin Berlin and performed according to the Second Declaration of Helsinki. All participating women provided written informed consent.

Women in both groups did not differ in their age, BMI, parity, smoking status, body composition, or physical activity status (as measured by the bioelectrical impedance and 6-min walking test). However, the time interval from the most recent pregnancy was slightly shorter in the post-preeclamptic group (2.00 ±1.00 years vs. 4.00 ± 0.25 years; p < 0.01). The post-preeclamptic group showed a 13% increased left atrial (LA) end-diastolic volume (EDV) (37.69 ± 6.83 ml/m² vs. 33.27 ± 6.09 ml/m²; p = 0.03) and a 19% increased LA stroke volume (SV) (22.57 ± 5.83 ml/m² vs. 18.99 ± 5.22 ml/m²; p = 0.04) (all normalized to body surface area [BSA]), with a slight increase in left ventricular (LV) hypertrophy because LV SV normalized to BSA was 47.28 ± 7.03 ml/m² versus 51.30 ± 6.33 ml/m² (p = 0.05) and the LV remodeling index was 0.59 ± 0.11 versus 0.54 ± 0.08 (p = 0.06) (Figure 1). Associations between history of preeclampsia and changes in LA dimensions became even stronger after adjustment for BMI, age, parity, diastolic blood pressure, smoking status, and post-partum interval. The adjusted β coefficient for prediction of LA EDV was 14.03 ml (95% confidence interval: 6.56 to 21.50) (p < 0.01); the adjusted β-coefficient for prediction of LA SV was 10.69 ml (95% confidence interval: 3.99 to 17.38; p < 0.01). The associations between LV remodeling and history of preeclampsia disappeared after correction for diastolic blood pressure. Enlarged LA area size was already found in women with preeclampsia during the acute phase of the pregnancy disorder (2). Our findings pointed toward LA enlargement as a persistent pathophysiological residue sustained by preeclampsia and corroborated the hypothesis that cardiac alterations in post-preeclamptic women were persistent and did not resolve after a complicated pregnancy. According to the American Society of Echocardiography and the European Association of Echocardiography guidelines on evaluation of diastolic function, the recommended upper normal LA volume indexed to BSA is 34 ml/m².
FIGURE 1 Changes in Cardiac Dimensions and Function in Women After Preeclampsia as Detected by CMR

(A) Spider plot showing alterations in cardiac dimensions and function in women after preeclampsia. Data are expressed as fold changes compared with the control group and normalized to body surface area (BSA). (B) Group differences in left atrial (LA) end-diastolic volume (EDV)/BSA (a), LA stroke volume (SV)/BSA (b), left ventricular (LV) SV/BSA (c), and LV remodeling index (RI) (d) between post-preeclampsia (PPE) and control groups. Differences were tested by independent samples t-test or Mann-Whitney U-test, as appropriate. *p < 0.05; **p < 0.01 versus control group. CMR = cardiovascular magnetic resonance; EF = ejection fraction; ESV = end-systolic volume; RA = right atrium; RV = right ventricular.
In this study, post-preeclamptic women showed LA volume/BSA above this cutoff. LA enlargement is an integrative marker of pathophysiological processes, such as LV diastolic dysfunction, atrial fibrillation, and stroke (3,4).

CMR tissue tracking analysis revealed reduced global radial strain (GRS) and global circumferential strain (GCS) in the post-preeclamptic group (mean difference ± SEM: 4.56 ± 2.08%; p = 0.03; and −1.60 ± 0.71%; p = 0.03, respectively). Abnormalities in myocardial mechanics could occur before or simultaneously with hypertrophic remodeling and typically predated the development of cardiac fibrosis (5).

We did not detect differences in focal or diffuse myocardial tissue composition between the groups.

CMR imaging is able to identify subtle cardiac end-organ damage, indicating diastolic dysfunction as early as 2 years after preeclampsia. LV deformation measured with GCS and GRS was significantly reduced in post-preeclamptic women. A history of preeclampsia is associated with cardiac end-organ damage (LA remodeling), even after adjustment for blood pressure and other clinical and demographic characteristics. Follow-up studies are needed to identify the critical window when morphological tissue differentiation (e.g., progression to myocardial fibrosis or inflammation) occurs in post-preeclamptic patients.

Anna Birukov, MSc
Stephanie Wiesemann, MD
Michaela Golic, MD
Andras Balogh, MD, PhD
Lajos Marko, MD, PhD
Natalia Rakova, MD, PhD
Nicola Wilck, MD
Edyta Blaszczzyk, MD
Carolin Lim
Sara Weiss
Kristin Kräker, PhD
Nadine Haase, PhD
Alina Frolova, MSc
Jan Stener Jørgensen, MD, PhD
Steffen Daub, MD
Dominik N. Müller, PhD
Florian Herse, PhD
Jeanette Schulz-Menger, MD
Ralf Dechend, MD

*Experimental and Clinical Research Center (ECRC) Lindenberger Weg 80 1325 Berlin Germany
E-mail: jeannette.schulz-menger@charite.de https://doi.org/10.1016/j.jcmg.2020.01.005

© 2020 by the American College of Cardiology Foundation. Published by Elsevier.

Please note: Drs. Schulz-Menger and Dechend contributed equally to this work. Dr. Herse was supported by the Deutsche Forschungsgemeinschaft (grant HE 6249/5-1). Dr. Golic was a participant of the Clinician Scientist Program funded by the Charité - Universitätsmedizin Berlin and the Berlin Institute of Health (BIH). Dr. Kräker was supported by a BIH translational PhD project grant. Dr. Schulz-Menger has been a member of the advisory board for Bayer. All other authors have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Bellamy L, Casas JP, Hingaran AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.
2. Vaught AJ, Kovell LC, Szymanski LM, et al. Acute cardiac effects of severe pre-eclampsia. J Am Coll Cardiol 2018;72:1-11.
3. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
4. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol 2014;63:2335-45.
5. Bianco CM, Farjo PD, Ghaffar YA, Sengupta PP. Myocardial mechanics in patients with normal LVEF and diastolic dysfunction. J Am Coll Cardiol 2020;13:258-71.

LETTER TO THE EDITOR

Magnetic Resonance to Diagnose Cardiac Amyloidosis

Is it Already Time to Discard Contrast Agents?

We have read with interest the paper by Baggiano et al. (1) regarding the use of noncontrast cardiac magnetic resonance (CMR) as a diagnostic tool for cardiac amyloidosis (CA). The notion that CA can be excluded when native T1 is <1,036 ms and confirmed when T1 is >1,164 ms, thus limiting contrast administration to 58% of patients with intermediate T1 values (1), is appealing, but several issues deserve consideration. First, given the variability of T1 measurements among different CMR systems and T1 mapping sequences, each center should compare the proposed T1 cutoffs with its cohort of healthy normal subjects or identify its optimal cutoffs. Moreover, native T1 was measured in the basal to mid septum of the 4-chamber map, a method that on the 1 hand is straightforward and reliable, but on the other hand does not take into account the regional distribution of T1 values across all ventricular segments. Second, the positive and negative predictive values of these cutoffs are heavily influenced by disease prevalence in the population studied (2), which in this case...
corresponds to the percentage of patients referred to CMR who have CA. As a result, when the availability of CMR examination is more limited, and patients are referred to CMR only for a strong suspicion of CA, the positive predictive value of the proposed cutoffs will increase and the negative predictive value will decrease. Therefore, the 1,036 ms cutoff will become less effective for ruling out CA, and the 1,164 ms will more effective for ruling in the disease. The diagnostic accuracy of these cutoff is also variable across different amyloid subtypes: for example, among patients with amyloid transthyretin amyloidosis, who had significantly lower T1 values than those with amyloid light chain (AL) amyloidosis (1,133 ± 58 ms vs. 1,166 ± 64 ms; p < 0.001), the 1,036 ms rule-out cutoff represents a z-score of −1.67, corresponding to around 5% of true positive amyloid transthyretin patients that would be missed by this algorithm.

Third, the cutoffs would have been more accurately selected based on likelihood ratios (LRs), with LR−((1 − sensitivity)/specificity) < 0.1 identifying an optimal rule-out cutoff, and LR+ (sensitivity/ (1 − specificity)) > 10 denoting an optimal rule-in cutoff (3). Fourth, cardiac amyloid light-chain (AL) amyloidosis was diagnosed based on “the combination of typical features on CMR and biopsy-proven systemic AL amyloidosis on cardiac or noncardiac biopsy,” whereas endomyocardial biopsy was performed only in 5% of the whole population (1). This diagnostic approach then relied heavily on the sensitivity of noncardiac biopsy (although only 73% of patients with systemic amyloidosis have a positive periumbilical fat biopsy) (4), the expertise of the CMR reader (who must establish whether CMR features are typical of AL amyloidosis), and disease stage (which influences the likelihood of typical findings on CMR). Finally, noncontrast CMR would be particularly valuable for patients with contraindication to contrast medium because of advanced chronic kidney disease, but only 45 patients (5%) had an estimated glomerular filtration rate <30 ml/min/1.73 m² (1). A dedicated assessment of these patients in a larger cohort would then be valuable.

In conclusion, the study by Baggiano et al. (1) is an important first step in the assessment of noncontrast CMR in patients with suspected CA, but we feel that further studies are needed before this technique could be proposed for everyday clinical practice.

Alberto Aimo, MD*
Michele Emdin, MD, PhD
Andrea Barison, MD, PhD

*Institute of Life Sciences
Scuola Superiore Sant’Anna
Piazza Martiri della Libertà 33
56124 Pisa
Italy
E-mail: albertoaimo@libero.it OR a.aimo@santannapisa.it
https://doi.org/10.1016/j.jcmg.2020.01.030
© 2020 by the American College of Cardiology Foundation. Published by Elsevier.

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

REFERENCES
1. Baggiano A, Boldrini M, Martinez-Naharro A, et al. Noncontrast magnetic resonance for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol Cardiovasc Imaging 2020;13:69–80.
2. Ranganathan P, Aggarwal R. Common pitfalls in statistical analysis: Understanding the properties of diagnostic tests - Part I. Perspect Clin Res 2018; 9:40–3.
3. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ 2004;329: 168–9.
4. Bogov B, Lubomirova M, Kiperova B. Biopsy of subcutaneous fatty tissue for diagnosis of systemic amyloidosis. Hippokratia 2008;12:236–9.

THE AUTHORS REPLY:

We thank Dr. Aimo and colleagues for their interest in our study (1). Regarding the variability of native T1 across different sites, we fully agree that local reference ranges are needed. We would go further and highlight the importance of phantom quality control to ensure drift between the time of reference range creation and scanning (2). The authors highlight the use of a single region in the midseptum. We agree that such a method is only suitable for diffuse disease. This was discussed in the second mapping consensus document, which recommended more regions of interest for focal disease, and, in amyloidosis, highlighted the need of a single region of interest preferably in 4-chamber, as, with the base-to-apex gradient, a single midventricle short axis can be misleading (3). The authors point out that diagnostic testing requires a Bayesian approach to interpretation and the relative merits of positive predictive value, negative predictive value, and likelihood ratios (LRs). The authors suggest that the cutoffs would have been more accurately selected based on LR, with LR −<0.1 and LR + >10 denoting optimal rule-out and rule-in cutoffs, respectively. The native T1 cutoffs of 1,036 ms and 1,164 ms correspond indeed to a LR of 0.02 and to a LR of 32. This approach should be taken further because several problems are related to the frequent use, in modern medicine, of cutoffs. The field should be encouraged to consider future methods...
incorporating multidimensional approaches to probability including additional imaging and clinical features. Deep learning approaches (ridge regression, random forest, etc.) will be needed to develop best possible ways of interpretation. In terms of diagnostic gold standard, we agree that the sensitivity of a periumbilical fat pad biopsy is only 73% (3). However, individual patients in this cohort had multiple biopsies with at least 1 positive biopsy in each individual case. We fully agree with the issues surrounding the truth standard for disease and selection bias induced in cohorts based on the use of invasive or noninvasive imaging; all approaches have limits, and our work therefore serves as a standard that should be prospectively tested at other, ideally multicenter sites. Finally, although only a relatively small proportion of patients had an estimated glomerular filtration rate <30 ml/min/1.73 m², 45 patients with suspected cardiac amyloidosis and estimated glomerular filtration rate <30 ml/min/1.73 m² represents the biggest group with these characteristics ever published so far.

In conclusion, whilst we fully acknowledge that this study has certain limitations, it represents the largest study on the utility of native T1 mapping for the diagnosis of cardiac amyloidosis and as such, is an important step for the field.

Andrea Baggiano, MD†
Michele Boldrini, MD†
Ana Martinez-Naharro, MD
Tushar Kotecha, MBChB
Aviva Petrie, BSc (Hons), MSc
Tamer Rezk, MBBS
Maurizio Gritti, MD
Cristina Quarta, MD, PhD
Daniel S. Knight, MBBS, MD (Res)

Ashutosh D. Wechalekar, MD, PhD
Helen J. Lachmann, MD
Stefano Perlini, MD, PhD
Gianluca Pontone, MD, PhD
James C. Moon, MD
Peter Kellman, PhD
Julian D. Gillmore, MD, PhD
Philip N. Hawkins, PhD
Marianna Fontana, MD, PhD*

*National Amyloidosis Centre
University College London
Royal Free Campus
Rowland Hill Street
London NW3 2PF
United Kingdom
E-mail: m.fontana@ucl.ac.uk

https://doi.org/10.1016/j.jcmg.2020.02.024
© 2020 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Please note: †Drs. Baggiano and Boldrini contributed equally to this work. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.

REFERENCES

1. Baggiano A, Boldrini M, Martinez-Naharro A, et al. Noncontrast magnetic resonance for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol Img 2020;13:69–80.

2. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1,T2,T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19:75.

3. Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. Eur Heart J 2017;38:1905-8.
“Black swan” events are by definition unexpected (even if the “black swan” has been visible before) and come with catastrophic consequences. One such occurrence is the current coronavirus pandemic, which is likely to have a considerable impact on the practice of medicine in as yet unknown ways. A likely consequence will be a significant economic downturn and constrained budgets, resulting in even higher pressure to optimize our diagnostic and therapeutic pathways. To survive the cost pressure, diagnostic studies will have to evolve significantly: they must be fast, use the most cost-effective approach, and result in a therapeutic consequence or management guidance. Shorter examinations require focus on the core question, standardized image acquisition and procedures, and rapid, increasingly automated data analysis and reporting. Cost-effectiveness requires more research, but also using the knowledge we have to reduce unnecessary diagnostic and therapeutic procedures.

In this issue of iJACC, Rijlaarsdam-Hermsen et al. (1) provide information on one strategy that seems promising and yet opens up new questions. The investigators used stress-only perfusion cardiovascular magnetic resonance (CMR) in patients with stable chest pain and coronary artery calcium (CAC) scores >0 to guide patients to invasive angiography. They found obstructive coronary artery disease (CAD) in only 3% of patients in the group without typical angina and CAC scores <100 and 16% among patients with nonanginal chest pain and CAC scores ≥400. This is the first study showing the advantage of using CAC as a gatekeeper for CMR stress testing, and it adds to the evidence that rest perfusion can be safely skipped in most perfusion CMR studies, a strategy also supported by the latest Society for Cardiovascular Magnetic Resonance standardized acquisition consensus (2). D’Angelo et al. (3) previously demonstrated that scar imaging (late gadolinium enhancement) can be done with a 0.1-mmol dose of a gadolinium-based contrast agent without loss of image quality or diagnostic information and a shorter wait time between contrast injection and scar imaging. Cine imaging can be performed after perfusion and before late gadolinium enhancement, reducing total scan time for a fully standardized CMR examination to approximately 15 to 20 min. Such comprehensive examinations must become the standard for CMR to increase patient throughput and reduce costs. However, the core question remains: how can we maximize the clinical effectiveness of diagnostic procedures in patients with chest pain? Several strategies are currently advocated: the use of better pretest probability assessments (4), incorporating gatekeeping methods (1), sequential imaging (5), value-added testing such as computed tomographic (CT) fractional flow reserve and CT perfusion (6), and finally hybrid imaging (7) of various forms. However, all of these must now pass once again through the critical filter of economics and newer evidence such as that from the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial (8).

One possible change that could find new proponents might be avoiding most diagnostic imaging for CAD. However, no imaging would make sense only if we would stop revascularizing patients with stable angina and would accept giving up on risk assessment (both excluding high-risk anatomy such as left main coronary artery and detecting high event
risk), as well as making a correct diagnosis. Such consequences are neither perceivable without some imaging, nor would they contribute to the best possible patient management. Coronary calcium, ischemia, and vulnerable plaques are all important predictors of future events, and knowledge about them can guide the type and extent of risk-modifying therapy and lifestyle changes.

The proponents of a “one-stop shop” approach could argue for cardiac computed tomography in all patients with chest pain independent of pre-test likelihood, supported by CT fractional flow reserve in those with potentially hemodynamically significant coronary stenoses. This approach is advocated by the United Kingdom’s National Institute for Health and Care Excellence guidelines (9) and is based mainly on the notion that exclusion of CAD can be done with limited effort and costs using CT angiography. Advances in CT perfusion (10) could substantially buttress this argument. This approach is also supported by the high negative predictive value of CT angiography and data from the SCOT-HEART (Scottish Computed Tomography of the HEART Trial) trial (11), demonstrating that knowledge of coronary anatomy and plaques improves outcomes. In contrast, this approach has the disadvantage that the majority of patients will have negative results on computed tomography, which requires nephrotoxic contrast agents, a rare, but not negligible prevalence of allergic reactions and some ionizing radiation, thus also adding significantly to the overall cost. CMR imaging allows a combination of function, scar imaging, mapping, and perfusion and can serve as an attractive “go to” test; it is well validated, allows precise quantitation and a high degree of automation (12), and is one of the few tests that shows non-inferiority compared with an invasive fractional flow reserve-based strategy for the management of stable CAD (13). However, it will have to overcome limited availability and the need for a high degree of expertise.

A Bayesian approach might continue to find favor despite evidence against it (9). Performing computed tomography in the lower range of pre-test likelihoods and stress imaging in patients with intermediate to high pre-test probability is advocated by the European Society of Cardiology guidelines on chronic coronary syndromes (14). This approach is highly evidence based for the diagnosis of CAD, as it allows a reliable rule-out in the lower pre-test probability group and a rule-in with testing for significant CAD and significant ischemia in the intermediate to high pre-test likelihood group. According to these guidelines, patients with very high pre-test likelihood should proceed directly to invasive angiography. Two recent studies challenge these guidelines. First, MR-INFORM (MR Perfusion Imaging to Guide Management of Patients With Stable Coronary Artery Disease) (13) has demonstrated that patients with high pre-test likelihood can also be safely guided by noninvasive perfusion CMR, thus reducing unnecessary invasive angiography in this specific patient group. Second, the ISCHEMIA trial (8) challenges the need to assess patients invasively for prognostic reasons but reveals utility for relief on symptoms. Symptomatic relief, however, requires a correct diagnosis of the underlying problem, which can frequently be determined using CMR imaging with a combination of function, scar imaging, mapping, and perfusion.

Sequential imaging, where one proceeds to the next test only if a low-cost efficient test produces abnormal results, has found some favor and is supported by at least 1 small randomized controlled trial (15). A combination of CAC scoring and perfusion CMR is a variation that strategy and now has evidentiary support (1). This approach reduces the need for invasive angiography, while minimizing the need for perfusion scanning in those with low calcium burden, further shortening the CMR study and eliminating the need to apply vasodilator stress in a considerable group of patients. Using biomarkers alone for predicting CAD has been less than conclusive so far (16), and a combination of imaging and biomarkers might improve performance. Hybrid imaging—using multiple modalities around the same time (either individually or on the same machine, as with positron emission tomography/computed tomography or positron emission tomography/magnetic resonance)—is attractive but may not adequately fulfill its promise at this time (17).

Value-added testing, using CMR or CT angiography, might become one of the more attractive avenues for cost-effective imaging. Some strategies might provide important insights regarding anatomy, physiology (18), blood flow quantitation, microvascular health (19), and information about the vessel wall (20) and prognosis in the same test environment. Both computed tomography and CMR allow this, and rapid advances, including automation (12, 21) and machine learning (22), may allow novel paradigms. For example, it would be interesting to investigate whether a CAC scan (without CT coronary angiography) and a noncontrast CMR study could be combined in a specific group of patients, obviating the need for contrast injection or even vascular access for a stressor administration (23), which could
considerably increase patient throughput and offer testing at a much lower cost than currently possible. Whether such multimodality approaches can save costs needs to be determined.

We need to start focusing less on the diagnosis of CAD and guidance toward revascularization and concentrate more on strategies and their effectiveness to establish a final diagnosis and optimally and individually guide patient management in a cost-effective way.

ADDRESS FOR CORRESPONDENCE: Dr. Y. Chandrashekhar, Division of Cardiology, University of Minnesota/VA Medical Center, Cardiology (111C), 1 Veterans Drive, Minneapolis, Minnesota 55417. E-mail: shekh003@umn.edu.

REFERENCES

1. Rijlaarsdam-Hermans, Lo-Kiang-Shioe M, van Domburg RT, et al. Stress-Only Adenosine CMR Improves Diagnostic Yield in Stable Symptomatic Patients With Coronary Artery Calcium. J Am Coll Cardiol Img 2020;13:1152–60.
2. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson 2020;22:17–8.
3. D’Angelo T, Grigoratos C, Mazzitelli S, et al. High-throughput gadobutrol-enhanced CMR: a time and dose optimization study. J Cardiovasc Magn Reson 2017;19:83.
4. Adamson PD, Newby DE, Hill CL, et al. Comparison of international guidelines for assessment of suspected stable angina: insights from the PROMISE and SCOT-HEART. J Am Coll Cardiol Img 2018;11:1301–10.
5. Maamitty T, Stenstrom I, Bax JJ, et al. Prognostic value of coronary CT angiography with selective PET perfusion imaging in coronary artery disease. J Am Coll Cardiol Img 2018;11:1361–70.
6. Celeng C, Leiner T, Maurovich-Horvat P, et al. Anatomical and functional CT for diagnosing hemodynamically significant coronary artery disease: a meta-analysis. J Am Coll Cardiol Img 2019;12:1316–25.
7. Liwa R, Vantobel J, Roval D, et al., for the EVINCI Study Investigators. Multicentre multi-device hybrid imaging study of coronary artery disease: results from the Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischaemic Heart Disease (EVINCI) hybrid imaging population. Eur Heart J Cardiovasc Imaging 2016;17:951–60.
8. Maron DJ, Hochman JS, Reynolds HR, et al., for the ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395–407.
9. National Institute for Health and Care Excellence. Surveillance report 2016—stable angina: management (2011) NICE guideline CG126. London, United Kingdom: National Institute for Health and Care Excellence; 2016.
10. Nakamura S, Kitagawa K, Goto Y, et al. Incremental prognostic value of myocardial blood flow quantified with stress dynamic computed tomography perfusion imaging. J Am Coll Cardiol Img 2019;12:1379–87.
11. SCOT-HEART Investigators, Newby DE, Adamson PD, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med 2018;379:924–33.
12. Rotecha T, Martinez-Naharro A, Boldrini M, et al. Automated pixel-wise quantitative myocardial perfusion mapping by CMR to detect obstructive coronary artery disease and coronary microvascular dysfunction. J Am Coll Cardiol Img 2019;12:1958–69.
13. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med 2019;380:2418–28.
14. Knudt J, Wijesunge RS, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019;100:1606.
15. Lubbiers M, Coenen A, Kofflard M, et al. Comprehensive cardiac CT with myocardial perfusion imaging versus functional testing in suspected coronary artery disease. J Am Coll Cardiol Img 2018;11:1625–36.
16. Januzzi JL, Suchindran S, Coles A, et al. on behalf of the PROMISE Investigators. High-sensitivity troponin I and coronary computed tomography in symptomatic outpatients with suspected CAD. J Am Coll Cardiol Img 2019;12:1047–55.
17. Rizvi A, Han D, Danad I, et al. Diagnostic performance of hybrid cardiac imaging methods for assessment of obstructive coronary artery disease compared with stand-alone coronary computed tomography angiography. J Am Coll Cardiol Img 2018;11:589–99.
18. Ahmadi A, Leipsic J, Øvrehus KA, et al. Lesion-specific and vessel-related determinants of fractional flow reserve beyond coronary artery stenosis. J Am Coll Cardiol Img 2018;11:521–30.
19. Liu A, Wijesunge RS, Liu JM, et al. Diagnosis of microvascular angina using cardiac magnetic resonance. J Am Coll Cardiol 2018;71:969–79.
20. Lee S-E, Chang H-J, ung J-M. Effects of statins on coronary aththerosclerotic plaques. J Am Coll Cardiol Img 2018;11:1475–84.
21. Hsu L-Y, Jacobs M, Benovoy M, et al. Diagnostic performance of fully automated pixel-wise quantitative myocardial perfusion imaging by cardiovascular magnetic resonance. J Am Coll Cardiol Img 2018;11:697–707.
22. Lijens G, Ciompi F, Wolterink JM, et al. State-of-the-art deep learning in cardiovascular image analysis. J Am Coll Cardiol 2019;12:1549–65.
23. Nakamori S, Fahmy A, Jang J, et al. Changes in myocardial native T1 and T2 after exercise stress. J Am Coll Cardiol Img 2020;13:667–80.