Journal Scan

H. Nagaraja Rao

Introduction

Cardiac science and technology are changing rapidly with the emergence of newer diagnostic and therapeutic options every other day. It is pivotal to all of us who are involved in managing patients with cardiovascular diseases to getting updated with these new things. In the current issue of the journal scan, articles are collected between January and June 2021, from the different cardiovascular subjects like cardiac imaging, heart failure, interventions, and basic sciences, which could have an impact on current clinical practice.

Cardiovascular Imaging

Right Ventricular Functional Abnormalities in Arrhythmogenic Cardiomyopathy

Feddo P Kirkels, Øyvind H Lie, Maarten J Cramer, Monica Chivulescu, Christine Rootwelt-Norberg, Folkert W Asselbergs, Arco J Teske, Kristina H Haugaa

Abstract

Objectives: This study aimed to perform an external validation of the value of right ventricular (RV) deformation patterns and RV mechanical dispersion in patients with arrhythmogenic cardiomyopathy (AC). Second, this study assessed the association of these parameters with life-threatening ventricular arrhythmia (VA).

Background: Subtle RV dysfunction assessed by echocardiographic deformation imaging is valuable in AC diagnosis and risk prediction. Two different methods have emerged, the RV deformation pattern recognition and RV mechanical dispersion, but these have neither been externally validated nor compared.

Methods: We analyzed AC probands and mutation-positive family members, matched from 2 large European referral centers. We performed speckle tracking echocardiography, whereby we classified the subtricuspid deformation patterns from normal to abnormal and assessed RV mechanical dispersion from 6 segments. We defined VA as sustained ventricular tachycardia, appropriate implantable cardioverter-defibrillator therapy, or aborted cardiac arrest.

Results: We included 160 subjects, 80 from each center (43% proband, 55% women, age 41-17 years). VA had occurred in 47 (29%) subjects. In both cohorts, patients with a history of VA showed abnormal deformation patterns (96% and 100%) and had greater RV mechanical dispersion (53-30 ms vs. 30-21 ms; P < .001 for the total cohort). Both parameters were independently associated to VA (adjusted odds ratio: 2.71 [95% confidence interval: 1.47-5.00] per class step-up, and 1.26 [95% confidence interval: 1.07-1.49]/10 ms, respectively). The association with VA significantly improved when adding RV mechanical dispersion to pattern recognition (net reclassification improvement 0.42; P = .02 and integrated diagnostic improvement 0.06; P = .01).

Conclusions: We externally validated 2 RV dysfunction parameters in AC. Adding RV mechanical dispersion to RV deformation patterns significantly improved the association with life-threatening VA, indicating incremental value.

Comments: AC is predominantly an autosomal inherited disease characterized by fibrofatty replacement of heart muscle usually involving RV free wall, but biventricular and left ventricular dominant variants have been described. Fibrofatty replacement is a substrate for VA and they account for 5% to 10% of sudden cardiac deaths (SCD) in individuals less than 65 years of age. Diagnosis of AC in the early stage of the disease is a critical task to avoid SCD. Electrocardiographic and echocardiographic changes like RV outflow tract dilatation, regional aneurysms, and dyskinesias are the markers of advanced disease. Currently available tools, including cardiac magnetic resonance imaging (MRI), doesn’t identify regional and subtle RV function.

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Hence, there is an urgent need for newer echocardiographic tools to identify subtle phenotypic expression in early AC. The current study done by Feddo P Kirkles focused on new echocardiographic tools like mechanical dispersion and deformation patterns to predict VA risk in the early stages of AC patients. The former focuses on heterogeneity in global RV contraction with a good prediction for progressive disease, while the latter reflects the focal substrate of a particular segment (RV subtricuspid area). Both together have an excellent incremental value in predicting life-threatening VA. Hence, these can be used as an alternative for predicting VA risk in centers lacking a cardiac MRI facility.

**Heart Failure**

*Biomarker-Based Risk Prediction of Incident Heart Failure in Prediabetes and Diabetes*

*J Am Coll Cardiol HF.* 2021, March;9(3):215-223.

Ambarish Pandey, Muthiah Vaduganathan, Kershaw V Patel, Colby Ayers, Christie M Ballantyne, Mikhail N Kosiborod, Mercedes Carnethon, Christopher DeFilippi, Darren K McGuire, Sadiya S Khan, Melissa C Caughey, James A de Lemos, Brendan M Everett

**Abstract**

**Objectives:** This study evaluated the application of a biomarker-based risk score to identify individuals with dysglycemia who are at high risk for incident heart failure (HF) and to inform allocation of effective preventive interventions.

**Background:** Risk stratification tools to identify patients with diabetes and prediabetes at highest risk for HF are needed to inform cost-effective allocation of preventive therapies. Whether a biomarker score can meaningfully stratify HF risk is unknown.

**Methods:** Participants free of cardiovascular disease from 3 cohort studies (ARIC [Atherosclerosis Risk In Communities], DHS [Dallas Heart Study], and MESA [Multi-Ethnic Study of Atherosclerosis]) were included. An integer-based biomarker score included high-sensitivity cardiac troponin T ≥ 6 ng/l, N-terminal pro-B-type natriuretic peptide ≥ 125 pg/mL, high-sensitivity C-reactive protein ≥ 3 mg/L, and left ventricular hypertrophy by electrocardiography, with 1 point for each abnormal parameter. The 5-year risk of HF was estimated among participants with diabetes and prediabetes across biomarker score groups (0-4).

**Results:** The primary analysis included 6,799 participants with dysglycemia (diabetes: 33.2%; prediabetes: 66.8%). The biomarker score demonstrated good discrimination and calibration for predicting 5- and 10-year HF risk among prediabetes and diabetes cohorts. The 5-year risk of HF among subjects with a biomarker score of ≤ 1 was low and comparable to participants with euglycemia (0.78%). The 5-year risk for HF increased in a graded fashion with an increasing biomarker score, with the highest risk noted among those with scores of ≥ 3 (diabetes: 12.0%; prediabetes: 7.8%). The estimated number of HF events that could be prevented using a sodium-glucose cotransporter-2 inhibitor per 1,000 treated subjects over 5 years was 11 for all subjects with diabetes and ranged from 4 in the biomarker score zero group to 44 in the biomarker score ≥ 3 group.

**Conclusions:** Among adults with diabetes and prediabetes, a biomarker score can stratify HF risk and inform allocation of HF prevention therapies.

**Comments:** The burden of diabetes mellitus is increasing rapidly in India and poses a major health problem. Patients with diabetes have a 2-fold higher risk of developing heart failure (HFpEF, HFrEF), which is responsible for 1.8 million hospitalizations annually and causes financial constraints.

Heart failure (HF) is a progressive disorder initiated after an index event. Neurohormonal, cytokine, fibrinogen, natriuretic, and insulin signaling pathways are triggered, resulting in a series of end-organ changes in the myocardium (left ventricular remodeling).

The study by Ambaresh Pandey et al developed a biomarker scoring system, which classifies the diabetic population into very-low, low, intermediate, and high-risk groups for developing HF over the next 5 years. The high-risk group comprised <10% of the study subjects, but they accounted for 35% of HF cases over 5 years. The study sets a stage that could change the landscape of HF prevention. They propose using sodium-glucose cotransporter 2 inhibitors in high-risk groups, can effectively prevent HF. Restricting usage of such costly drugs to high-risk groups will help in the cost-effective treatment of other groups.

**Electrophysiology**

*Long-Term Outcomes in Patients With a Left Ejection Fraction #15% Undergoing Cardiac Resynchronization Therapy*

*Am Coll Cardiol EP.* 2021;7:36-46.

John Rickard, Divyang Patel, Carolyn Park, Joseph E Marine, Sunil Sinha, WH Wilson Tang, Niraj Varma, Bruce L Wilkoff, David Spragg

**Abstract**

**Objectives:** This study aimed to determine the long-term outcomes and predictors of left ventricular (LV) ejection fraction (LVEF) improvement in patients with severe cardiomyopathies undergoing cardiac resynchronization therapy (CRT).
**Background:** Whether patients with severe LV dysfunction benefit from CRT or have reached a point in disease severity past the point at which CRT is beneficial is unknown.

**Methods:** We collected clinical and echocardiographic data on 420 patients with an LVEF of #15% and a QRS duration of $120 \text{ ms}$ undergoing CRT at the Cleveland Clinic and 2 hospitals in the Johns Hopkins Health System between April 2003 and May 2014. Multivariate models were created to determine factors associated with response to CRT, defined as an absolute improvement in LVEF of >5%, and survival free of LVAD and heart transplant. Procedure-related deaths were also collected.

**Results:** A total of 298 patients had pre- and appropriately timed post-CRT echocardiograms, of whom 145 (48.7%) met the criteria for response. In multivariate analysis, LV size and left bundle branch block (LBBB) were associated with response. Among the most dilated quintile (LV end-diastolic diameter [LVEDD] of >7.8 cm), 30.4% met the criteria for response. In multivariate analysis, smaller LV end-diastolic dysfunction and presence of LBBB were associated with improved survival free of heart failure and LVAD over a mean follow-up period of 5.2 years. There were no procedure-related deaths.

**Conclusions:** Patients with severe LV dysfunction respond to CRT, although at a lower rate compared to traditional CRT candidates. Smaller LV size and LBBB are important predictors of positive outcomes in this population. Even among the most dilated patients, 30.4% realized a meaningful improvement in LVEF with CRT. The CRT implant procedure itself appears well tolerated.

**Comments:** Heart failure is a common problem in India, incidence (4.9 lakhs-1.8 million) and prevalence (1.3-4.6 million) are projected to rise due to the increasing aging population and heart failure risk factors like coronary artery disease, hypertension, obesity, and diabetes. Currently available therapeutic options for severely depressed left ventricular function and enlarged ventricles pose a challenging task. They include guideline-directed medical therapy, advanced therapies like CRT, LVAD, and cardiac transplantation.

The current study by John Rickard et al focused on patients with very severely reduced LVEF (<15%) who were under-represented in previous clinical trials. The study demonstrates CRT as the safest procedure, without any procedure-related mortality. Patients who underwent CRT in the study had a reasonable chance to improve cardiac function without LVAD and cardiac transplantation. In such patients, the procedure also improved survival benefits and quality of life. A major limitation of the study is that it doesn’t contain a CRT control group. However, further prospective studies are needed.

**Structural**

**Transfemoral Transcatheter Tricuspid Valve Replacement With the EVOQUE System: A Multicenter, Observational, First-in-Human Experience**

*J Am Coll Cardiol Intv. 2021;14:501-511.*

Neil P Fam, Ralph Stephan von Bardeleben, Mark Hensey, Susheel K Kodali, Robert L Smith, Jörg Hausleiter, Geraldine Ong, Robert Boone, Tobias Ruf, Isaac George, Molly Szerlip, Michael Näbauer, Faeex M Ali, Robert Moss, Vinayak Bapat, Katharina Schnitzler, Felix Kreidel, Jian Ye, Djeven P Deva, Michael J Mack, Paul A Grayburn, Mark D Peterson, Martin B Leon, Rebecca T Hahn, John G Webb

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**Conclusions:** Patients with severe LV dysfunction respond to CRT, although at a lower rate compared to traditional CRT candidates. Smaller LV size and LBBB are important predictors of positive outcomes in this population. Even
among the most dilated patients, 30.4% realized a meaningful improvement in LVEF with CRT. The CRT implant procedure itself appears well tolerated.

Comments: Tricuspid regurgitation (TR) is one of the most common valvular heart lesions encountered in clinical practice. Prevalence of any TR is 65% to 85% of patients undergoing routine echocardiography. Significant TR (≥2/4) comprises 1.2% to 10.2% of these. TR is classified as primary, which is rare or secondary to left-sided heart failure (more common). Severe TR, whether symptomatic or asymptomatic, carries a poor prognosis when left untreated. Medical therapy is of limited efficacy. Surgical interventions like valve replacement or repair have significant morbidity and mortality, while transcatheter leaflet repair (valve repair or valve-in-valve procedure) emerged as a viable alternative to surgical intervention.

TR interventions are infrequently performed due to high morbidity and mortality and a lack of prospective data supporting improved outcomes. It is also presumed that managing left-sided heart disease would decrease TR.

The current research paper by Neil P Fam et al demonstrates EVOQUE Transfemoral Transcatheter Tricuspid Valve Replacement (TTVR) had higher technical success compared to other transcatheter valve repairs in reducing TR grade without any MACE events at 30-day follow-up. TTVR had a broader patient population when compared to Transcatheter tricuspid valve repair (torrential massive TR, tricuspid valve tethering, and larger tricuspid annulus). TTVR is reserved for patients with more advanced diseases. The major limitations are the small sample size, the study being observational without a standardized protocol for patient management.

Cardiovascular Interventions

Pharmacodynamic Effects of Prehospital Administered Crushed Prasugrel in Patients With ST-Segment Elevation Myocardial Infarction

J Am Coll Cardiol Intv. 2021;14:1323-1333

Rosanne F Vogel, Ronak Delew, Dominick J Angiolillo, Jeroen M Wilschut, Miguel E Lemmert, Roberto Diletti, Ria van Vliet, Nancy WPL van der Waarden, Rutger-Jan Nuis, Valeria Paradies, Dimitrios Alexopoulos, Felix Zijlstra, Gilles Montalescot, Mitchell W Krucoff, Nicolas M van Mieghem, Pieter C Smits, Georgios J Vlachojannis

Abstract

Objectives: This study sought to compare the pharmacodynamic effects of prehospital administered P2Y12 inhibitor prasugrel in crushed versus integral tablet formulation in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI).

Background: Early dual antiplatelet therapy is recommended in STEMI patients. Yet, onset of oral P2Y12 inhibitor effect is delayed and varies according to formulation administered.

Methods: The COMPARE CRUSH (Comparison of Prehospital Crushed Versus Uncrushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Interventions) trial randomized patients with suspected STEMI to crushed or integral prasugrel 60-mg loading dose in the ambulance. Pharmacodynamic measurements were performed at 4 time points: before antiplatelet treatment, at the beginning and end of pPCI, and 4 h after study treatment onset. The primary endpoint was high platelet reactivity at the end of pPCI. The secondary endpoint was impact of platelet reactivity status on markers of coronary reperfusion.

Results: A total of 441 patients were included. In patients with crushed prasugrel, the occurrence of high platelet reactivity at the end of pPCI was reduced by almost one-half (crushed 34.7% vs. uncrushed 61.6%; odds ratio ¼ 0.33; 95% confidence interval ¼ 0.22-0.50; P <.01).

Comments: Antiplatelets are the cornerstone in the immediate management of ST-segment elevated myocardial infarction (STEMI). Patients with STEMI are at risk of thrombotic events during and after percutaneous coronary intervention (PCI). High platelet reactivity (HPR) has been postulated to play a major role. Despite prompt administration of antiplatelets, suboptimal action of antiplatelets could be due to delayed gastrointestinal absorption. Multiple studies have been done to try and bridge the early gap of HPR by decreasing gastrointestinal absorption time by using crushed oral antiplatelets.

The current study (COMPARE CRUSH) by Rosanne F Vogel et al compared prehospital usage of crushed versus uncrushed Prasugrel in patients with STEMI undergoing primary PCI. They observed, nearly two-thirds of patients who took crushed Prasugrel tablets had good pharmacodynamic effects with HPR <150, two-fold higher TIMI III flow in infarct related artery on coronary angiogram during primary PCI. However, this didn’t improve the early marker of coronary perfusion (ST-segment resolution after primary PCI), indicates the role of platelet inhibition is less contributing in preserving coronary microcirculation. It appears crushing prasugrel partly bridges the gap of HPR. However, solution to this issue is the ready availability of Cangrelor and Larger trails comparing Cangrelor and fast-acting crushed forms of prasugrel and ticagrelor on HPR.