Layer-specific analysis of dobutamine stress echocardiography for the evaluation of coronary artery disease

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Abstract

Although dobutamine stress echocardiography (DSE) is a well-defined tool for the diagnosis of coronary artery disease (CAD), false-negative and false-positive results still occur. This study investigated the diagnostic role of layer-specific analysis using 2-dimensional speckle-tracking echocardiography (STE) during DSE.

A total of 121 patients who underwent DSE and showed normal wall motion and ejection fraction during baseline echocardiography were enrolled. All patients underwent coronary angiography after DSE within 2 weeks. The patients were divided into the following 4 groups according to DSE results and CAD status: negative DSE with no significant CAD (n = 73), positive DSE with significant CAD (n = 16), negative DSE with significant CAD (n = 17), and positive DSE with no significant CAD (n = 15). Layer-specific global longitudinal strain (GLS) was assessed in the endocardium, mid-myocardium, and epicardium by STE techniques.

Patients with significant CAD were older, more male and showed higher glucose level compared to patients without CAD. But coronary risk factors and previous medications were not different between patients with and without CAD. There were no significant differences in whole myocardium or layer-specific GLS found in the baseline echocardiography. During recovery echocardiography, endocardial GLS was significantly different between patients with and without CAD, regardless of the DSE results. A receiver-operating characteristic curve analysis showed that endocardial GLS (>-16%) was superior for identifying significant CAD during the DSE recovery stage. Diagnostic accuracy was improved by applying the results of endocardial GLS compared with visual estimation of DSE.

The assessment of layer-specific strain by STE during DSE was feasible, and the evaluation of poststress endocardial function is a more sensitive tool for the detection of CAD.

Abbreviations: 2D = 2-dimensional, AUC = areas under the curve, CAD = coronary artery disease, CI = confidence interval, DSE = dobutamine stress echocardiography, ECG = electrocardiography, EF = ejection fraction, GLS = global longitudinal strain, HR = hazard ratio, LV = left ventricular, ROC = receiver-operating characteristic, RWMA = regional wall motion abnormalities, STARD = Standards for Reporting Diagnostic Accuracy, STE = speckle-tracking echocardiography, WMSI = wall motion score index.

Keywords: dobutamine, echocardiography, myocardial strain, sensitivity, specificity

1. Introduction

Cardiac imaging is still undergoing development to improve diagnosis and avoid unnecessary invasive procedures. Although conventional echocardiography is widely used as the first-line modality in most clinical circumstances, its resting images have some limitations regarding the detection of coronary artery disease (CAD). Recently, several studies have shown that 2-dimensional (2D) speckle-tracking echocardiography (STE) can detect early changes in the myocardium, which may be beneficial as an additional CAD diagnostic tool.[1,2] Current guidelines recommend exercise electrocardiography (ECG) for patients with suspected CAD,[3] however, exercise testing has low sensitivity and specificity and is not suitable for patients with poor exercise tolerance or with baseline ECG abnormalities.[4] Pharmacologic stress testing, such as dobutamine stress echocardiography (DSE), is a good alternative diagnostic tool, but it requires extensive clinical experience to diagnose regional wall motion abnormalities (RWMA) visually.[5] DSE is not a physiologic stress test, but it has some advantages over treadmill echocardiography, including the capture of clearer poststress images. Since myocardial ischemia rapidly induces contractile dysfunction, detecting postischemic stunned myocardium may improve diagnostic accuracy in patients with suspected CAD. Recently, a more detailed layer-specific analysis of myocardial strain was introduced, which may allow for the early diagnosis of myocardial...
ischemia. In this study, we hypothesized that an additional layer-specific analysis of STE using visual DSE estimation is feasible, and that it will improve the diagnostic accuracy of significant CAD. To address this question, the differences in endocardial, mid-myocardial, and epicardial strain were evaluated in patients with negative, positive, false-negative, and false-positive DSE results.

2. Methods

2.1. Study population

Between January 2011 and December 2014, 2398 patients underwent DSE in a single center. Eligibility criteria included patients undergone DSE and coronary angiography within 2 weeks as a result of clinical decision making, had normal left ventricular (LV) wall motion by visual estimation, and had a normal ejection fraction (EF) (>60%) determined by the modified Simpson method at rest on transthoracic echocardiography. Patients with RWMA at baseline echocardiography, previous documented CAD, prior revascularization therapy, cardiomyopathy, significant valvular disease, pericardial effusion, a history of cardiac surgery, or inadequate images were excluded. The details are described in Fig. 1. Finally 121 patients were enrolled in this study. Based on the results of invasive coronary angiography and DSE, patients were classified into the following 4 groups: Group 1: negative DSE results and no significant CAD, n=73; Group 2: positive DSE results and significant CAD, n=16; Group 3: negative DSE results and significant CAD, n=17; Group 4: positive DSE results and no significant CAD, n=15. Figure 2 shows representative cases of each group. The study protocol was approved by our institutional ethics committee (KMC IRB 1119-03), and informed consent was waived. The study was conducted using the format recommended by the Standards for Reporting Diagnostic Accuracy (STARD) statement.

2.2. Dobutamine stress echocardiography

Resting echocardiography and DSE studies were performed with the patient in the left lateral decubitus position using a commercially available system (Vivid E9, General Electric Vingmed, Milwaukee, WI) equipped with a 3.5-MHz transducer. Digital loops were stored on the hard disk of the echocardiography machine for online and offline analyses, and were transferred to a workstation (EchoPac 6.1.3, General Electric Vingmed) for offline analysis. Standard techniques were used to obtain M-mode, 2D images, and Doppler measurements in accordance with the American Society of Echocardiography guidelines. Beta-blockers and calcium channel blockers (nondihydropyridines) were discontinued at least 24 hours before the test. The standard 17-segment model was used for wall-motion analyses at rest and at each DSE stage. A positive DSE result was defined as wall motion impairment by at least 1 grade in at least 2 adjacent segments at any dose of dobutamine. The wall motion score index (WMSI) was assessed according to the 17 segments model.

2.3. Layer-specific analysis of 2-dimensional speckle-tracking echocardiography

Speckle-tracking analysis using dedicated software (EchoPac 6.1.3, GE Medical Systems, Horten, Norway) was used to assess endocardial, mid-myocardial, epicardial, and whole myocardial strain. The software analyzes motion by tracking speckles (natural acoustic markers) in the ultrasonic image in 2 dimensions. Layer-by-layer longitudinal strains were automatically obtained from the apical long axis slices (2- and 4-chamber, and long axis views). All segmental values were averaged to produce a global longitudinal strain (GLS) for each myocardial layer and the whole myocardium. Layer-specific GLS analyses were performed at rest, at 10 μg/kg/min, and during recovery. The peak stage analysis was rejected due to low frame rates and poor reproducibility. Segments that failed to track properly were manually adjusted by an experienced operator. The mean frame rate of the obtained images was 70 fps (range 50–90 fps). All echocardiographic and strain analyses were performed separately in a blinded fashion to the other patient data. The reproducibility of this method was reported previously.
2.4. Coronary angiography and clinical outcomes

All study participants underwent coronary angiography. CAD assessment was determined visually for each stenosis with multiple projections, avoiding side branch overlaps and fore-shortening of relevant coronary stenosis. Significant obstructive CAD was defined as >70% luminal narrowing of a major epicardial coronary artery or >50% luminal narrowing of the left main coronary artery. \(^{(13)}\) Angiographic data were analyzed by 2 experienced investigators who were blind to the DSE results.

Clinical follow-up was performed via retrospective chart review or telephone contact. Hospital records were screened for clinical events to confirm the obtained information. The outcome events for this study were all caused mortality.

2.5. Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows ver. 17.0 (SPSS, Inc., Chicago, IL). A 2-sided \( P < 0.05 \) was considered significant. Continuous variables, presented as means ± standard deviations, were evaluated for normal distribution and then compared using Student \( t \) test or analysis of variance. Continuous parameters with a skewed distribution were logarithmically transformed. Categorical variables, presented as frequencies and percentages, were compared using the Chi-square or Fisher exact test. Receiver-operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values for continuous variables. The results are expressed as areas under the curve (AUC) or the 95% confidence interval (CI) for this area. The comparison of 2 ROC curves was compared by DeLong test.\(^{(14)}\) The optimal cutoff value was defined as the point associated with the highest sensitivity and specificity. The overall mortality-free survival rates were compared using the Kaplan–Meier analysis, and the event rates were compared using the log-rank test. A Cox proportional hazard model was used to determine the association with mortality and the results are expressed with a hazard ratio (HR) and 95% CI.

3. Results

3.1. Baseline demographics

The clinical characteristics of patients are summarized in Table 1. Patients with significant CAD were significantly older, more male, higher serum creatinine level. Demographics of 4 groups according to DSE results and CAD status also presented as Supplement Table 1, http://links.lww.com/MD/B185. Patients with Group 2 showed significantly older than others. In coronary angiography, more right coronary artery lesion and distal stenosis could be noted in Group 3.
3.2. Myocardial changes in response to dobutamine

Table 2 shows the results of conventional echocardiography. At baseline, there were no significant differences in LV EF, end-diastolic volume, or systolic volume among the 4 groups. However, E/E' was significantly higher in Groups 2 and 4. After infusion of 10 μg/kg/min dobutamine, there were no significant differences except WMSI. In recovery stage, elevated E/E' and higher WMSI could be noted in Groups 2 and 4.

The effects of dobutamine on strain in each layer are shown in Table 3. Baseline echocardiography did not show any strain differences among the 3 layers. After low dose dobutamine infusion, patients in Group 1 showed augmented 3-layer-specific strain compared with Groups 2, 3, and 4. There were no significant differences in strain parameters among Groups 2, 3, and 4 during low-dose dobutamine echocardiography. After the peak stage of dobutamine infusion, layer-specific strain recovered to baseline levels in Groups 1 and 4. However, the recovery of endocardial and mid-myocardial strain was impaired in Groups 2 and 3, even though heart rates had recovered to baseline rates.

3.3. Prediction of CAD

Optimum cutoff values for separation of patients with and without subsequent significant CAD were obtained by ROC analysis using endocardial GLS assessed during DSE (Fig. 3).

Endocardial GLS >−16% at recovery phase was selected as an important predictor of significant CAD (Z = −2.168, P = 0.03).

As shown in Fig. 1, the sensitivity, specificity, positive predictive value and negative predictive value of DSE were 48% (95% CI: 31%–66%), 83% (95% CI: 73%–90%), 52% and 81%, respectively. If positive DSE results were defined as recovery of endocardial GLS >−16%, the sensitivity, specificity, positive predictive value and negative predictive value were 85% (95% CI: 68%–95%), 92% (95% CI: 84%–97%), 79% and 94%, respectively. When visual estimation and recovery-stage endocardial GLS were considered together, the sensitivity, specificity, positive predictive value and negative predictive value were 91% (95% CI: 76%–98%), 91% (95% CI: 83%–96%), 79% and 96%, respectively.

Figure 4 shows the differences in endocardial GLS according to CAD location. In patients with left anterior descending coronary artery lesions, endocardial GLS was significantly impaired after low-dose infusion of dobutamine infusion. However, the differences of endocardial GLS could be observed only in recovery-stage endocardial GLS in patients with right coronary or left circumflex artery lesions.

3.4. Clinical outcomes

Median follow-up date was 1501 days (1039–2163 days). There were 13 cardiac deaths (4 patients in Group 1; 5 patients

| Table 1: Demographic characteristics. |
|---------------------------------------|
|                                       |
| **Significant CAD (n = 33)**          |
| **No significant CAD (n = 88)**       |
| **P**                                |
|---------------------------------------|
| Age, y                                |
| 70.1 ± 7.9                            |
| 63.1 ± 9.6                            |
| < 0.01                                |
| Gender (male, %)                      |
| 19 (57.6%)                            |
| 30 (34.1%)                            |
| 0.03                                  |
| Body surface area, kg/m²              |
| 1.63 ± 0.15                           |
| 1.65 ± 0.14                           |
| 0.68                                  |
| Risk factors                          |
| Hypertension (n, %)                   |
| 27 (81.8%)                            |
| 59 (67.0%)                            |
| 0.17                                  |
| Diabetes mellitus (n, %)              |
| 12 (36.4%)                            |
| 20 (22.7%)                            |
| 0.20                                  |
| Dystymia (n, %)                       |
| 10 (30.3%)                            |
| 22 (25.0%)                            |
| 0.72                                  |
| Current smoker (n, %)                 |
| 7 (21.2%)                             |
| 21 (23.9%)                            |
| 0.95                                  |
| Cerebral infarction (n, %)            |
| 12 (36.4%)                            |
| 21 (23.9%)                            |
| 0.25                                  |
| Peripheral artery disease (n, %)      |
| 3 (9.1%)                              |
| 3 (5.4%)                              |
| 0.42                                  |
| Past medications                     |
| Aspirin (n, %)                        |
| 18 (54.5%)                            |
| 29 (33.0%)                            |
| 0.05                                  |
| Clopidogrel (n, %)                    |
| 7 (21.2%)                             |
| 11 (12.5%)                            |
| 0.36                                  |
| ACE inhibitor or ARB (n, %)           |
| 12 (36.4%)                            |
| 36 (40.9%)                            |
| 0.80                                  |
| Beta blocker (n, %)                   |
| 9 (27.3%)                             |
| 22 (25.0%)                            |
| 0.96                                  |
| Calcium antagonist (n, %)             |
| 15 (45.5%)                            |
| 35 (37.5%)                            |
| 0.56                                  |
| Nitrates (n, %)                       |
| 2 (6.1%)                              |
| 8 (9.1%)                              |
| 0.87                                  |
| Statin (n, %)                         |
| 11 (33.3%)                            |
| 33 (37.5%)                            |
| 0.83                                  |
| Oral hypoglycemic agent (n, %)        |
| 7 (21.2%)                             |
| 17 (19.3%)                            |
| 0.99                                  |
| Insulin (n, %)                        |
| 4 (12.1%)                             |
| 3 (3.4%)                              |
| 0.16                                  |
| Reasons for DSE                       |
| Preoperation (n, %)                   |
| 8 (24.2%)                             |
| 24 (27.3%)                            |
| 0.61                                  |
| ECG abnormality (n, %)                |
| 3 (9.1%)                              |
| 13 (14.8%)                            |
| 0.99                                  |
| Chest pain (n, %)                     |
| 22 (66.7%)                            |
| 51 (58.0%)                            |
| Laboratory findings                  |
| Glucose, mg/dL                        |
| 113.5 (96.0–144.0)                    |
| 100.0 (90.0–115.5)                    |
| < 0.01                                |
| Creatinine, mg/dL                     |
| 0.9 (0.7–1.0)                         |
| 0.7 (0.6–0.9)                         |
| 0.03                                  |
| Total cholesterol, mg/dL             |
| 169.5 (146.0–189.5)                   |
| 168.0 (147.0–203.0)                   |
| 0.91                                  |
| Triglyceride, mg/dL                   |
| 110.5 (78.0–157.0)                    |
| 117.0 (88.5–164.5)                    |
| 0.37                                  |
| HDL cholesterol, mg/dL               |
| 46.9 ± 11.0                           |
| 48.4 ± 13.8                           |
| 0.59                                  |
| LDL cholesterol, mg/dL               |
| 108.6 ± 36.3                         |
| 106.7 ± 30.0                         |
| 0.79                                  |
| HbA1c, %                              |
| 5.8 (5.7–6.6)                         |
| 6.0 (5.6–6.4)                         |
| 0.80                                  |

Data are presented as n (%), means ± SD or median (range) unless otherwise indicated.

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; DSE = dobutamine stress echocardiography; ECG = electrocardiography; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; LDL = low density lipoprotein.
Recovery phase

Speckle-tracking echocardiography.

| GLS at resting state | Group 1 (n=73) | Group 2 (n=16) | Group 3 (n=17) | Group 4 (n=15) | P |
|----------------------|----------------|----------------|----------------|----------------|---|
| Whole myocardial strain | −18.6±0.9 | −18.1±1.1 | −17.8±1.3 | −18.6±0.7 | 0.51 |
| Subendocardial strain | −20.2±2.8 | −18.0±3.6 | −18.2±3.3 | −19.9±2.6 | 0.28 |
| Mid-myocardial strain | −14.5±3.7 | −14.4±3.1 | −14.5±2.9 | −15.1±2.2 | 0.90 |
| Epicardial strain | −9.7±3.9 | −9.0±2.5 | −9.9±2.8 | −10.9±3.1 | 0.36 |

| GLS at low dose dobutamine infusion | Group 1 (n=73) | Group 2 (n=16) | Group 3 (n=17) | Group 4 (n=15) | P |
|--------------------------------------|----------------|----------------|----------------|----------------|---|
| Whole myocardial strain | −21.2±3.1 | −16.2±2.9 | −17.2±2.3 | −15.5±3.1 | 0.02 |
| Subendocardial strain | −23.4±1.8 | −15.7±4.1 | −18.9±5.1 | −18.8±2.9 | <0.01 |
| Mid-myocardial strain | −19.1±4.0 | −13.5±5.0 | −12.7±4.1 | −13.4±3.1 | <0.01 |
| Epicardial strain | −15.4±2.9 | −10.7±5.4 | −9.7±4.1 | −8.5±2.4 | <0.01 |

| GLS at recovery phase | Group 1 (n=73) | Group 2 (n=16) | Group 3 (n=17) | Group 4 (n=15) | P |
|----------------------|----------------|----------------|----------------|----------------|---|
| Whole myocardial strain | −18.1±3.4 | −12.2±2.3 | −14.8±2.2 | −17.1±3.1 | <0.01 |
| Subendocardial strain | −21.7±3.0 | −11.4±3.0 | −14.1±2.3 | −16.5±3.5 | <0.01 |
| Mid-myocardial strain | −17.8±3.8 | −11.2±3.6 | −11.6±2.7 | −13.9±2.0 | <0.01 |
| Epicardial strain | −12.8±2.9 | −8.9±3.4 | −10.9±3.9 | −10.9±4.0 | 0.10 |

GLS = global longitudinal strain.
4. Discussion

The principal findings of this study were layer-specific strain analysis during DSE was feasible in patients with CAD, endocardial GLS during recovery was a sensitive parameter for CAD identification, and additional evaluation of endocardial GLS improved the diagnostic accuracy of DSE compared with standard DSE evaluation. Endocardial GLS during recovery was correlated with all-cause mortality.

DSE is an established decision making tool for evaluating CAD, myocardial viability, preoperative risk, valvular stenosis severity, and cardiac etiology of exertional dyspnea. But wall motion analysis is subjective, and requires a highly trained professional on image acquisition and interpretation. The ranges of sensitivity and specificity are not consistent from one study to another, and there was no significant increase in test accuracy between 1991 and 2006. To improve diagnostic accuracy, many studies tried to evaluate new technologies. The recently developed STE method has a great hope to advance test sensitivity, angle-independency, and quantitative evaluation of myocardial shortening, thickening, and lengthening by rapid generation of strain curves. Its additional advantages are feasibility, semi-automatically myocardial tracking, and quantitative evaluation of myocardial shortening, thickening, and lengthening by rapid generation of strain curves. In this study, whole and layer-specific GLS analysis on 3 phases of DSE for each patients took maximally 5 minutes.

Recent studies have demonstrated STE during DSE could serve as an adjunctive method for CAD assessment. In contrast to augmentation of strain with dobutamine in normal tissue, ischemic tissue showed reduction of systolic deformation components and increase of postsystolic component. These studies provided promising diagnostic and prognostic role of STE during DSE. But prior STE techniques only evaluated the overall myocardium. The heart muscle is composed of three layers, and the endocardial layer is known as most susceptible and first component of the ischemic cascade. Even myocardial deformation during a cardiac cycle occurs in several axes (i.e., radially, longitudinally, and circumferentially), longitudinal deformation is largely determined by endocardial fibers. It implies the

Figure 3. Receiver-operating characteristic curves to discrete significant CAD. AUC = area under curve, CAD = coronary artery disease, DSE = dobutamine stress echocardiography, GLS = global longitudinal strain.

Figure 4. Subendocardial GLS according to CAD location. (A) Control vs LAD lesion; (B) Control vs LCx lesion; (C) Control vs RCA lesion. CAD = coronary artery disease, GLS = global longitudinal strain, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.
assessment of endocardial longitudinal deformation rather than radial or circumferential parameters may be superior for earlier ischemia detection on DSE. Previous studies showed whole GLS assessment at rest is an independent predictor of significant CAD and significantly improves the diagnostic performance of the exercise test and DSE. However, no differences in GLS were found between patients with positive and negative DSE results in this study. The discrepancy between previous studies and ours may be explained by the study populations. The relatively low sensitivity and high specificity of DSE observed here suggests that this study included a low-risk population. The probability of CAD with typical chest pain is an important predictor of significant CAD compared with the results of stress tests. Voigt et al. also examined the effectiveness of strain imaging during DSE; however, they used Doppler imaging, which is limited by its angle dependency. They also suggested that the postsystolic shortening ratio could be an objective marker of ischemia during DSE. However, we found that this measure was less reproducible during the peak stress phase (interobserver variability, r = 0.74) compared with the recovery phase (interobserver variability, r = 0.92). Poor frame rate and rapid heart rate may also impact these results. Instead of whole myocardial GLS, less reproducible during the peak stress phase (interobserver variability, r = 0.74) compared with the recovery phase (interobserver variability, r = 0.92).

In this study, 15 patients with a positive DSE showed no significant CAD. As shown in Supplement Table 1, women were included in false-positive group in a relatively high proportion. For subjects presenting for evaluation of suspected ischemic symptoms, a diagnosis of normal coronary arteries is 5 times more common in women as compared to men. Microvascular dysfunction would be a key contributory mechanism for myocardial ischemia and RWMA. It is clinically important. Previous study showed women with no obstructive CAD and evidence of myocardial ischemia have a relatively poor prognosis compared with women with no obstructive CAD and no myocardial ischemia. But this study did not evaluate coronary blood reserve or other imaging tests to detect abnormal coronary microcirculation. As shown in Fig. 1, only 3 patients showed endocardial Gls impairment after peak stress. Due to small sample size and limited evaluation, we could not conclude the correlation of microvascular dysfunction and endocardial Gls. Further studies would be required to detect the unique endocardial function.

This study had a number of limitations. First, it was a retrospective study with inherent methodological restrictions. We could not control the reasons for DSE, which may have been important factors influencing the DSE results. From a single-center DSE cohort, only 5% of patients were enrolled in this study. As patients with Groups 2 and 4 were performed coronary angiography, we defined the significant CAD by coronary angiography, not by coronary computed tomography angiogram. As shown in Fig. 1, more than half of patients did not proceed further examination and be excluded from this study. Patients with Groups 1 and 3 underwent coronary angiography by the decision of each cardiologists even though DSE results were negative. The reasons were clinical suspicions such as unexplained angina symptom or ECG abnormality. Even we screened all of patients underwent DSE, angiographic referral bias, and unavoidable selection bias may have existed in this study needing larger multicenter studies to confirm the results. Second, we could not validate endocardial Gls in a prospective design. Further multicenter studies are needed. Finally, the differences in regional strain parameters were not evaluated; however, lengthening strain or postsystolic strain would be more

[Figure 5. Mortality-free survival curves by Kaplan–Meier analysis. (A) Significant differences were observed in patients with significant CAD (Groups 2 and 3) compared to patients without CAD (Groups 1 and 4). (B) Patients with worsened endocardial Gls (> −16%) after peak stress showed significantly higher mortality. (C) Similar mortality-free survival curves were noted in patients with RWMA or endocardial Gls > −16%. CAD = coronary artery disease, Gls = global longitudinal strain, RWMA = regional wall motion abnormality.]
complicated to measure in daily practice. Instead of these measurements, GLS was analyzed with ease and was illustrated by Bull’s eye mapping. Despite these drawbacks, the endocardial strain during the recovery phase may be a suitable method for detection of significant CAD.

References

[1] Geyer H, Caracciolo G, Abe H, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 2010;23:351–69. quiz 355–453.

[2] Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 2014;100:1673–80.

[3] Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCA/SCAI/SCAI 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 Anography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44–164.

[4] Fox K, Garcia MA, Ardissono D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341–81.

[5] Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress Echocardiography Expert Consensus Statement—Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur Heart J 2009;30:278–89.

[6] Adamu U, Schmitz F, Becker M, et al. Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters. Eur J Echocardiogr 2009;10:303–8.

[7] Becker M, Ocklenburg C, Atiok E, et al. Impact of infarct transmurality on layer-specific impairment of myocardial function: a myocardial deformation imaging study. Eur Heart J 2009;30:1466–76.

[8] Ishizu T, Seo Y, Baba M, et al. Impaired subendocardial wall thickening and post-systolic shortening are signs of critical myocardial ischemia in patients with flow-limiting coronary stenosis. Circ J 2011;75:1934–41.

[9] Sarvari SH, Haagaa KH, Zahid W, et al. Layer-specific quantification of myocardial deformation by strain echocardiography may reveal significant CAD in patients with non-ST-segment elevation acute coronary syndrome. JACC Cardiovasc Imaging 2013;6:535–44.

[10] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

[11] Woo JS, Kim WS, Yu TK, et al. Prognostic value of serial global longitudinal strain measured by two-dimensional speckle tracking echocardiography in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2011;108:340–7.

[12] Woo JS, Kim W, Ha SJ, et al. Cardioprotective effects of exenatide in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of exenatide myocardial protection in revascularization study. Arterioscler Thromb Vasc Biol 2013;33:2252–60.

[13] Eagle KA, Guyton RA, Davidson R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004;110:1168–76.

[14] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:857–65.

[15] Geleijnse ML, Krenning BJ, van Delft RM, et al. Factors affecting sensitivity and specificity of diagnostic testing: dobutamine stress echocardiography. J Am Soc Echocardiogr 2009;22:1199–208.

[16] Smisek OA, Torp H, Opdahl A, et al. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016;37:1196–207.

[17] Eek C, Grenne B, Brunvand H, et al. Strain echocardiography and wall motion score index predicts final infarct size in patients with non-ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging 2010;3:187–94.

[18] Biering-Sorensen T, Hoffmann S, Mogelvang R, et al. Myocardial strain analysis by 2-dimensional speckle tracking echocardiography improves diagnostics of coronary artery stenosis in stable angina pectoris. Circ Cardiovasc Imaging 2014;7:58–65.

[19] Hanekom L, Cho KY, Leano R, et al. Comparison of two-dimensional speckle and tissue Doppler strain imaging during dobutamine stress echocardiography: an angiographic correlation. Eur Heart J 2007;28:176–72.

[20] Reant P, Labrousse L, Lafitte S, et al. Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. J Am Coll Cardiol 2008;51:149–57.

[21] Ng AC, Sitges M, Pham PN, et al. Incremental value of 2-dimensional speckle tracking strain imaging to wall motion analysis for detection of coronary artery disease in patients undergoing dobutamine stress echocardiography. Am Heart J 2009;158:836–44.

[22] Joyce E, Hoogslag GE, Al Amri I, et al. Quantitative dobutamine stress echocardiography using speckle-tracking analysis versus conventional visual analysis for detection of significant coronary artery disease after ST-segment elevation myocardial infarction. J Am Soc Echocardiogr 2015;28:1379–89.

[23] Bijnens B, Claus P, Weidemann F, et al. Investigating cardiac function using motion and deformation analysis in the setting of coronary artery disease. Circulation 2007;116:2453–64.

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

[25] Voigt JU, Exner B, Schmiedehausen K, et al. Strain-rate imaging during dobutamine stress echocardiography in ischemic conditions. J Am Coll Cardiol 2008;51:149–57.

[26] Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004;110:1168–76.

[27] Reant P, Labrousse L, Lafitte S, et al. Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. J Am Coll Cardiol 2008;51:149–57.

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

[29] Voigt JU, Exner B, Schmiedehausen K, et al. Strain-rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. Circulation 2003;107:2120–6.

[30] Reis SE, Holubkov R, Conrad Smith AJ, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. Am Heart J 2001;141:735–41.

[31] Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women’s Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:2983–9.

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