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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

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ischemia.[6–9] 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.

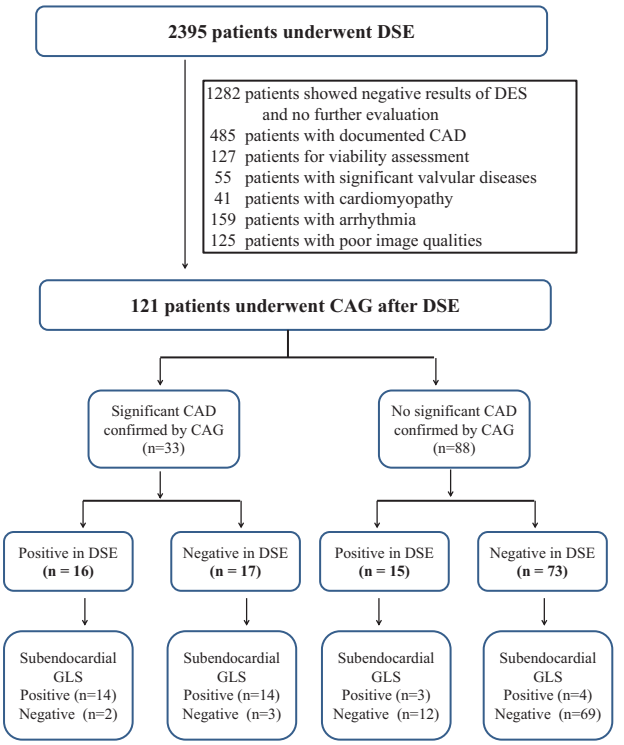

Figure 1. Study flow. DSE=dobutamine stress echocardiography, CAD=coronary artery disease, CAG=coronary angiography, GLS=global longitudinal strain.

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.[10] Beta-blockers and calcium channel blockers (nondihydropyridines) were discontinued at least 24 hours before the test. DSE image acquisition and analysis were performed according to the laboratory's standard protocol, using an initial dose of 10 μg/kg/min, which was gradually increased by 10 μg/kg/min every 3 minutes to a maximum dosage of 40 μg/kg/min. Intravenous atropine (0.2–0.4 mg every 2 min to a maximum of 2 mg) was infused to achieve the target heart rate, when needed. The endpoints were as follows: the maximum dose, heart rate ≥85% of the age-predicted maximum, limiting chest pain, headaches, vomiting, hypotension (systolic blood pressure <90 mm Hg), hypertension (systolic pressure ≥240 mm Hg), ventricular tachycardia, and sustained supraventricular tachycardia. Seven echocardiographic views [parasternal long- and short-axis (mitral valve, mid-papillary muscle, and apical levels), apical 2- and 4-chamber, and long axis views] were stored in a quad screen and continuous loop format on optical disks at rest and at the 10 μg/kg/min, peak dose, and recovery stages. 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.[10]

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.[11,12]

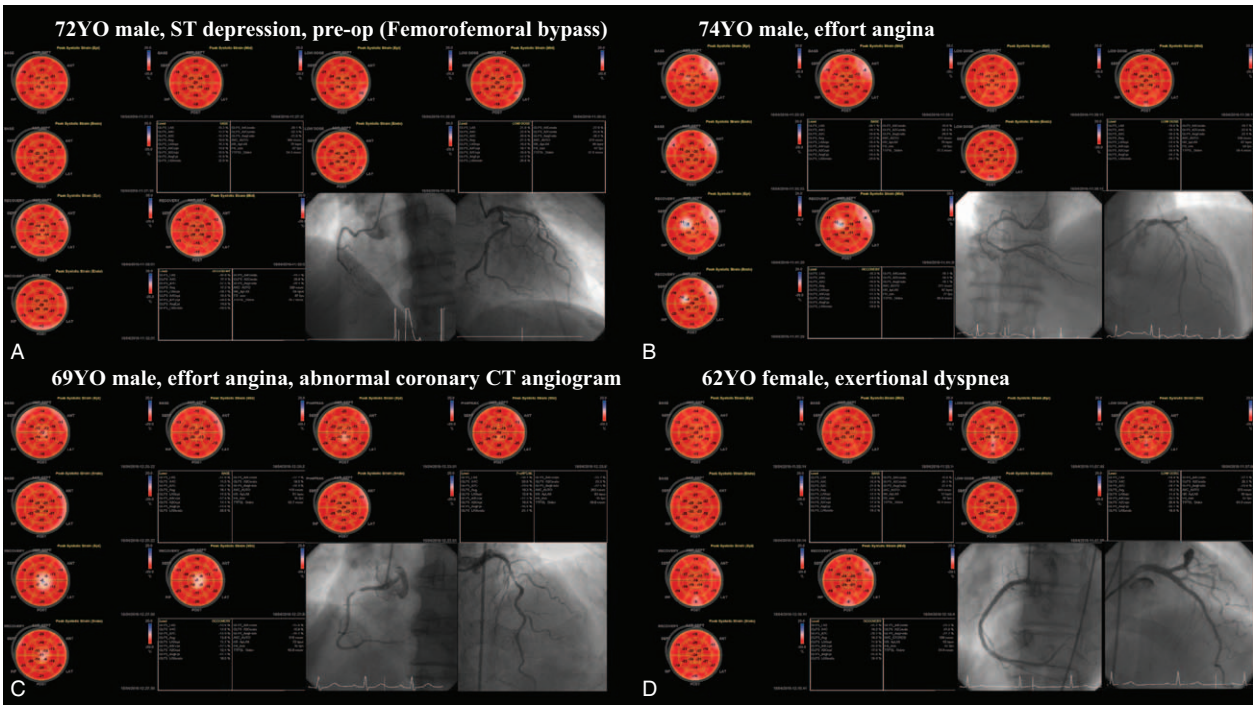

Figure 2. Representative cases. (A) A 72-year-old male with claudication was planned to perform femorofemoral bypass surgery. DSE demonstrated negative result (endocardial GLSs were −20.1%, −27.8%, and −19.7%; baseline, low dose, recovery, respectively). New change of ST depression in V3–V6 was noted at admission. Coronary angiogram revealed no significant stenosis. (B) A 74-year-old male complained chest pain during exercise. DSE demonstrated positive result with akinesia of LAD territory (endocardial GLSs were −16.9%, −19.7%, and −16.1%; baseline, low dose, recovery, respectively). Coronary angiogram revealed significant stenosis in mid LAD. (C) A 69-year-old male was evaluated with DSE and coronary CT angiography because of recurrent effort chest pain for 1 year. Even there were no RWMA on DSE (endocardial GLSs were −17.2%, −23.2%, and −15.8%; baseline, low dose, recovery, respectively), coronary CT angiography was revealed significant stenosis in RCA. Coronary angiogram revealed significant stenosis in RCA and LAD. (D) A 62-year-old female presented with a history of exertional shortness of breath over the last 1 month. DSE demonstrated positive result with akinesia of LAD territory (endocardial GLSs were −19.9%, −22.1%, and −23.1%; baseline, low dose, recovery, respectively). There was no significant stenosis on coronary angiogram. CT = computed tomography, DSE = dobutamine stress echocardiography, GLS = global longitudinal strain, LAD = left anterior descending coronary artery, RCA = right coronary artery, RWMA = regional wall motion abnormality, YO = year old.

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 foreshortening 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 analyzed 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.

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/m^2	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
Dyslipidemia (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 (3.4%)	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%)	0.98
Calcium antagonist (n, %)	15 (45.5%)	33 (37.5%)	0.56
Nitrate (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%)	
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 (148.0–189.5)	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.

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%), 80% and 94%, respectively. When visual estimation and recovery-stage endocardial GLS were consider 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 2

Conventional echocardiography.

	Group 1 (n=73)	Group 2 (n=16)	Group 3 (n=17)	Group 4 (n=15)	*P*
Resting state					
Systolic BP, mmHg	135.3±18.2	140.2±20.6	139.1±15.8	144.8±22.4	0.33
Diastolic BP, mmHg	80.5±11.1	76.5±14.6	79.0±8.7	77.1±12.8	0.55
Heart rate, beats/min	64.5±9.5	63.5±9.5	66.3±12.9	63.4±12.5	0.84
Ejection fraction, %	62.7±6.6	61.6±8.9	59.9±6.9	62.4±7.6	0.53
LV EDV, mL	66.2±26.1	69.9±20.1	59.2±15.2	65.1±23.2	0.56
LV ESV, mL	26.4±10.1	27.6±12.4	24.2±11.4	23.9±10.3	0.69
Deceleration time, ms	196.2±46.1	204.6±52.2	202.7±41.4	228.9±86.2	0.22
E/A	1.0±0.4	0.8±0.4	0.9±0.3	0.8±0.1	0.15
E/E′	11.8±3.4	15.1±7.4	11.8±3.7	15.9±7.5	0.01
WMSI	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	NA
Low dose dobutamine infusion					
Systolic BP, mmHg	152.1±30.4	146.7±20.6	151.0±18.5	166.3±31.7	0.26
Diastolic BP, mmHg	84.3±12.1	76.2±13.9	82.3±13.8	76.8±15.1	0.07
Heart rate, beats/min	69.8±13.9	68.6±12.5	70.5±20.1	69.8±13.4	0.98
Ejection fraction, %	67.4±6.9	66.6±9.6	65.6±9.5	68.9±8.1	0.71
LV EDV, mL	64.4±29.5	74.9±25.3	60.3±16.2	56.6±22.0	0.27
LV ESV, mL	23.0±9.2	25.6±13.3	21.3±10.3	19.3±9.1	0.38
Deceleration time, ms	191.1±54.4	210.2±53.1	206.3±57.4	197.6±73.4	0.60
E/A	0.9±0.5	0.9±0.5	0.9±0.5	0.8±0.3	0.82
E/E′	12.0±3.9	13.4±3.7	13.4±6.5	14.8±7.3	0.25
WMSI	1.0±0.0	1.03±0.05	1.0±0.0	1.0±0.2	< 0.01
Recovery phase					
Systolic BP, mmHg	133.7±30.4	134.9±26.9	136.9±26.9	144.0±19.3	0.67
Diastolic BP, mmHg	81.1±19.1	74.8±14.6	83.0±15.9	81.8±11.7	0.55
Heart rate, beats/min	87.2±22.3	88.7±18.9	83.3±18.8	82.3±14.5	0.75
Ejection fraction, %	62.7±6.3	64.2±7.8	62.3±6.4	61.6±8.5	0.78
LV EDV, mL	58.0±23.8	63.0±20.8	55.2±12.8	52.6±19.7	0.64
LV ESV, mL	24.6±12.3	24.4±12.0	20.9±6.5	22.1±8.9	0.63
Deceleration time, ms	172.9±40.6	161.2±44.9	191.1±48.7	180.6±56.4	0.28
E/A	0.8±0.4	0.7±0.3	0.7±0.2	0.7±0.1	0.45
E/E′	10.8±3.1	13.3±4.1	11.2±2.9	14.8±8.6	0.01
WMSI	1.0±0.0	1.24±0.18	1.0±0.0	1.15±0.12	< 0.01

A wave = late diastolic inflow velocity, BP = blood pressure, E wave = early diastolic inflow velocity, E′ = early diastolic medial mitral annular velocity, EDV = end-diastolic volume, ESV = end-systolic volume, LV = left ventricular, NA = nonassessable, WMSI = wall motion score index.

in Group 2; 4 patients in Group 3) and 2 noncardiac deaths (1 patient in Group 1; 1 patient in Group 4). Figure 5 shows the HR for all-cause mortality according to the results of DSE (A) and endocardial GLS after peak stress (B) and combination of wall motion analysis and endocardial GLS (C). Patients with RWMA or endocardial GLS $>-16\%$ showed higher mortality than patients with no RWMA and endocardial GLS $\leq -16\%$.

Table 3

Speckle-tracking echocardiography.

	Group 1 (n=73)	Group 2 (n=16)	Group 3 (n=17)	Group 4 (n=15)	*P*
GLS at resting state					
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					
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±3.1	−18.8±2.9	<0.01
Mid-myocardial strain	−19.1±4.0	−13.5±3.0	−12.7±4.1	−13.4±3.1	<0.01
Epicardial strain	−15.4±2.9	−10.7±3.4	−9.7±4.1	−8.5±2.4	<0.01
GLS at recovery phase					
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.

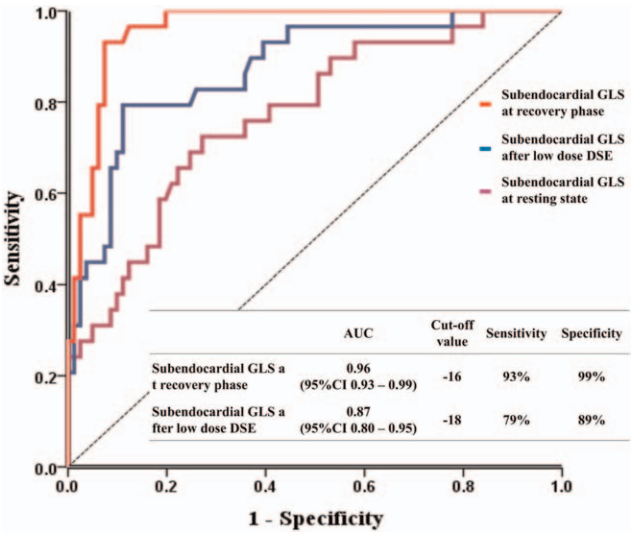

Figure 3. Receiver-operating characteristic curves to discrete significant CAD. AUC = area under curve, CAD = coronary artery disease, DSE = dobutamine stress echocardiography, GLS = global longitudinal strain.

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.[5] 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,[5] and there was no significant increase in test accuracy between 1991 and 2006.[15] To improve diagnostic accuracy, many studies tried to evaluate new technologies. The recently developed STE method has a great hope to advance test sensitivity. STE has been evaluated from subclinical to obvious diseases including diabetes, hypertension, myocardial ischemia, valvular disease, and heart failure.[11,16–18] Its additional advantages are feasibility, semi-automatically myocardial tracking, angle-independency, and quantitative evaluation of myocardial shortening, thickening, and lengthening by rapid generation of strain curves.[1,2] 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.[19–22] In contrast to augmentation of strain with dobutamine in normal tissue, ischemic tissue showed reduction of systolic deformation components and increase of postsystolic component.[23] 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.[11] It implies the

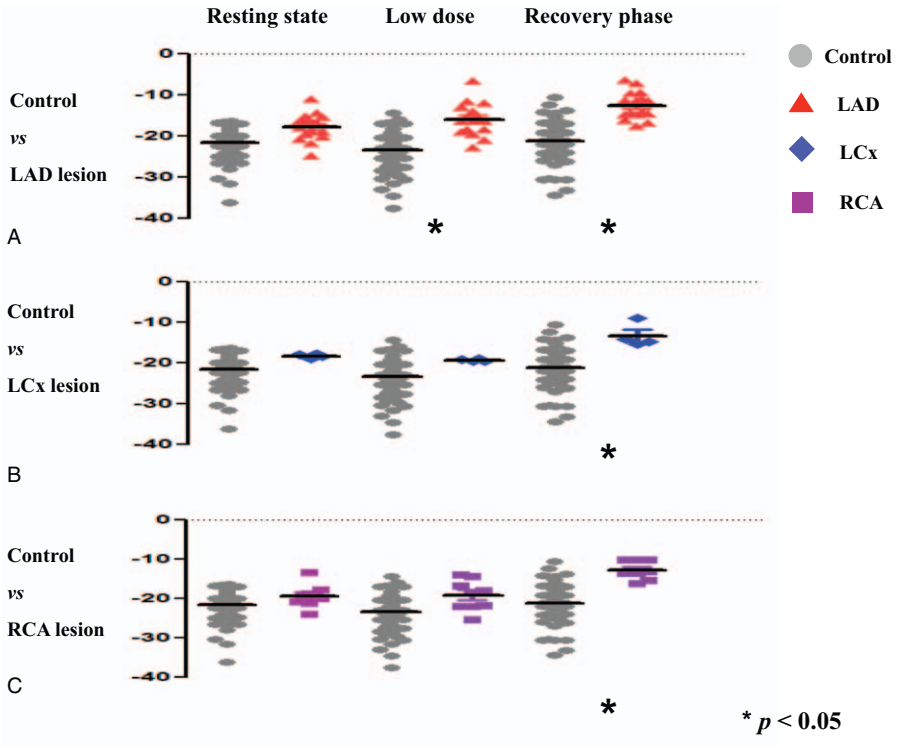

Figure 4. Subendocardial GLS according to CAD location. (A) Control vs LAD lesion; (B) Control vs LCx lesion; (C) Control vs RCA lesion. CAD = coronary artery disease, GLS = global longitudinal strain, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

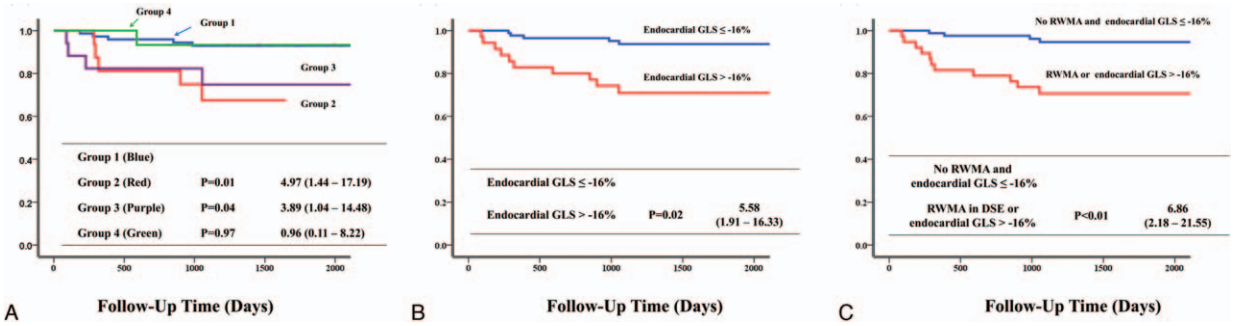

Figure 5. Mortality-free survival curves by Kaplan–Meier analysis. (A) Significant differences were observed in patients with significant CAD (Groups 2 and 3) compared to patients without CAD (Groups 1 and 4). (B) Patients with worsened endocardial GLS (>−16%) after peak stress showed significantly higher 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.

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.[18–22] 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.[3,24] Voigt et al[25] also examined the effectiveness of strain imaging during DSE; however, they used Doppler imaging, which is limited by its angle dependency.[16] 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, endocardial GLS would be more reasonable approach. Sarvari et al[9] conducted a layer-specific analysis in patients with non-ST segment elevation myocardial infarction, and showed that the degree of deformation in the endocardial layer was better at predicting CAD than was traditional LV EF.

This study aimed to determine whether myocardial analysis using STE and DSE could improve CAD diagnosis accuracy. Using layer-specific analysis, endocardial strain after peak stress was correlated significantly with the degree of coronary artery stenosis, and this method improved diagnostic accuracy compared with conventional DSE results. Visual assessment of wall motion relies mainly on evaluation of inward motion of the myocardium, whereas STE allows the evaluation of longitudinal myocardial shortening, which is not visible with the naked eye. As previously mentioned, we could note poor reproducibility during peak stage which leading to reject the results of peak stage analysis. Endocardial strain analysis during low dose dobutamine infusion showed slightly incremental value compared to whole myocardial strain analysis. But endocardial strain analysis after peak stress was superior and reasonable in ischemic detection. In this study, patients with false-negative results showed similar but earlier mortality compared to patients with positive results. As expected, misdiagnosis of CAD resulted in a fatal outcome. The combination of expert wall motion analysis and quantitative endocardial longitudinal strain analysis would improve diagnostic accuracy. Additionally, layer-specific strain analysis during DSE showed good feasibility and reproducibility as whole myocardial strain analysis.[19–22]

In this study, 15 patients with a positive DSE showed no significant CAD. As shown in Supplement Table 1, http://links.lww.com/MD/B185, women were included in false-positive group in a relatively high portion. 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.[26] 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.[27] But this study did not evaluated 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

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.

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