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SHORT COMMUNICATION

Regional layer-specific longitudinal peak systolic strain using exercise stress two-dimensional speckle-tracking echocardiography for the detection of functionally significant coronary artery disease

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Abstract
The present study aimed to investigate whether layer-specific regional peak-systolic longitudinal strain (LS) measurement on transthoracic echocardiogram (TTE) with exercise stress can be useful for the detection of functionally significant coronary artery disease as confirmed by invasive fractional flow reserve (FFR) in stable patients. This is a prospective analysis of 88 coronary arteries in 30 stable patients undergoing invasive FFR measurement and ergometer exercise stress TTE. Regional LS in the mid, endocardial and epicardial layers was calculated at rest, peak stress and early and late recovery phases after the exercise stress test. The endocardial-to-epicardial LS ratio was calculated as an indicator of endocardial-layer dependency of the left ventricular myocardium. Ischemic FFR defined as FFR ≤ 0.80 was observed in 33 of 88 coronary arteries. The mid-, endocardial- and epicardial-layer LS at early recovery (-15.4 ± 5.2 vs. $-13.0 \pm 4.4\%$, $P=0.040$; -15.7 ± 5.1 vs. $-13.2 \pm 4.5\%$, $P=0.029$; -14.6 ± 5.1 vs. $-12.4 \pm 4.0\%$, $P=0.038$, respectively) and the percent change in the endocardial-to-epicardial LS ratio from baseline to peak stress, early recovery, and late recovery phases ($1.5 \pm 11.2\%$ vs. $6.6 \pm 10.5\%$, $P=0.009$; $2.8 \pm 8.9\%$ vs. $7.1 \pm 12.6\%$, $P=0.002$; $5.2 \pm 8.8\%$ vs. $8.5 \pm 13.7\%$, $P=0.026$; respectively) were significantly more impaired in the ischemic territories (FFR ≤ 0.80) compared with the non-ischemic territories (FFR > 0.80). According to the receiver operating characteristic curve analysis, a combination of endocardial LS and percent change in the endocardial-to-epicardial LS ratio at early recovery phase plus visual evaluation of LV wall motion had incremental diagnostic value for the detection of the ischemic territory compared with visual evaluation alone (area under the curve = 0.752 and 0.618, $P=0.006$). The results of this study suggested that assessing layer-specific LS and the endocardial-to-epicardial LS ratio after exercise stress on speckle-tracking TTE may have potential for objective and quantitative evaluation in the assessment of myocardial ischemia. Further studies in a larger population are needed to confirm these findings.

Keywords Layer-specific longitudinal strain · Speckle tracking · Exercise stress echocardiography · Fractional flow reserve

Introduction

The presence of myocardial ischemia is an important prognostic indicator in patients with coronary artery disease (CAD). Fractional flow reserve (FFR) is a physiologic index invasively measured during coronary angiography and a well-validated surrogate for ischemia. The use of FFR has been shown to improve long-term clinical outcomes and quality of life while saving resources [1–4].

Stress transthoracic echocardiography (TTE) is a non-invasive functional diagnostic method for patients with suspected CAD. However, the evaluation of abnormalities of left ventricular (LV) function by qualitative estimation of wall thickening during stress TTE is somewhat subjective and requires a high level of expertise to obtain correct readings. Recent developments in echocardiography have paved the way for an objective and quantitative approach to evaluating the abnormal LV function. Previous studies have shown that two-dimensional (2D) strain using speckle-tracking TTE is accurate in the detection of LV contraction changes during ischemia [5–8], and in addition,

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speckle-tracking TTE during dobutamine stress could serve as an adjunctive method for CAD assessment [9–14]. Additional development in this field, a novel application of multilayer speckle-tracking TTE has facilitated the assessment of regional myocardial deformation at a layer-specific level [15]. As the longitudinal myocardial fibers located in the subendocardium are most susceptible to ischemia, layer-specific myocardial longitudinal strain (LS) can be a sensitive parameter for the diagnosis of functionally significant CAD [16, 17]. However, data are lacking on the application of layer-specific LS on exercise stress TTE for the diagnosis of myocardial ischemia.

Accordingly, the present study sought to investigate the utility of layer-specific regional peak-systolic LS measurement on TTE with exercise stress for the detection of functionally significant CAD as confirmed by invasive FFR in stable patients.

Methods

Study population

This was a prospective study that enrolled 30 patients with stable CAD at Chiba University Hospital. Patients were eligible if they had ≥ 50% stenosis in at least one major coronary artery confirmed by invasive coronary angiography, and were ≥ 20 years of age. The key exclusion criteria were as follows: left main coronary artery disease; atrial fibrillation; severe valvular heart disease; recent myocardial infarction (within 7 days); decompensated heart failure; advanced renal failure (estimated glomerular filtration rate ≤ 30 ml/min); severe left ventricular (LV) dysfunction (ejection fraction ≤ 30%); pregnancy; and inability to undergo exercise stress test. In addition, vessels with prior myocardial infarction were not included in the analysis. All patients underwent invasive coronary angiography with FFR and TTE with exercise stress within 30 days without clinical accidents as defined in the protocol.

Ethical approval for the study was obtained from the ethics committee in Chiba University (approval number 1639). All patients provided written informed consent. The present study was registered at the University Hospital Medical Information Network Clinical Trials Registry (number: UMIN000016059).

Resting and exercise stress echocardiography

Resting and exercise stress 2D TTE assessment was performed with the commercially available ultrasound device (Vivid E9, GE Healthcare, Horten, Norway) with a 3.5-MHz transducer. The conventional resting 2D TTE assessment was performed before stress testing as described previously [18].

Exercise stress was conducted utilizing a standard cycle ergometer. Participants pedaled in a left semi-lateral decubitus position at approximately 50–70 rounds per minute, following a multi-stage incremental method, starting at 0 W and increasing by 25 W every 3 min. Criteria for terminating the test were achieving a target heart rate response of 85% of the age-predicted maximum, development of wall motion abnormality, development of symptoms, severe ischemic electrocardiographic changes, systolic blood pressure > 240 mmHg, abnormal blood pressure reaction during stress, or significant arrhythmia. Beta-blockers were withdrawn for 2 days and long-acting nitrates the morning of the study.

Standard 2D grayscale images of three standard apical views (four-chamber, two-chamber, and apical long-axis) and parasternal long-axis and parasternal short-axis views at the level of mitral valve, papillary muscles, and apex were acquired at rest, at peak stress (during exercise), at early recovery phase (immediately to < 3 min after exercise), and at late recovery phase (5–8 min after exercise). Per protocol, three consecutive cardiac cycles per stage and view were digitally stored for later offline analysis. As for the visual analysis of wall motion, any wall motion abnormality induced by stress was considered a positive result, such as reduction or deterioration of systolic wall thickening or appearance of new or worsening of existing wall motion abnormalities during or after the stress protocol.

Layer-specific longitudinal strain analysis

Strain analysis was performed off-line using commercial imaging analysis software (EchoPac Version 113, GE Healthcare, Horten, Norway) as described previously [19] by two observers who were blind to the invasive coronary angiographic data, FFR values, and clinical data. The semi-automated algorithm provides the regional peak systolic LS for each LV segment in a 17-segment LV model [20], in each myocardial layer (Fig. 1). The percent change in the peak systolic LS parameters from rest to exercise was calculated as (peak systolic LS after exercise stress peak systolic LS at rest)/peak systolic LS at rest. For comparison with invasive coronary angiography, we used the conventional segmental division for the three main coronary territories [20]. In general, LS values are presented as negative values. Thus a greater value indicates more impaired regional function. The most impaired (i.e., the greatest) peak-systolic LS value in each coronary artery territory was adopted as the representative value of that territory. An average value of the vessel territory was used for the percent change in the LS parameters from rest to exercise.

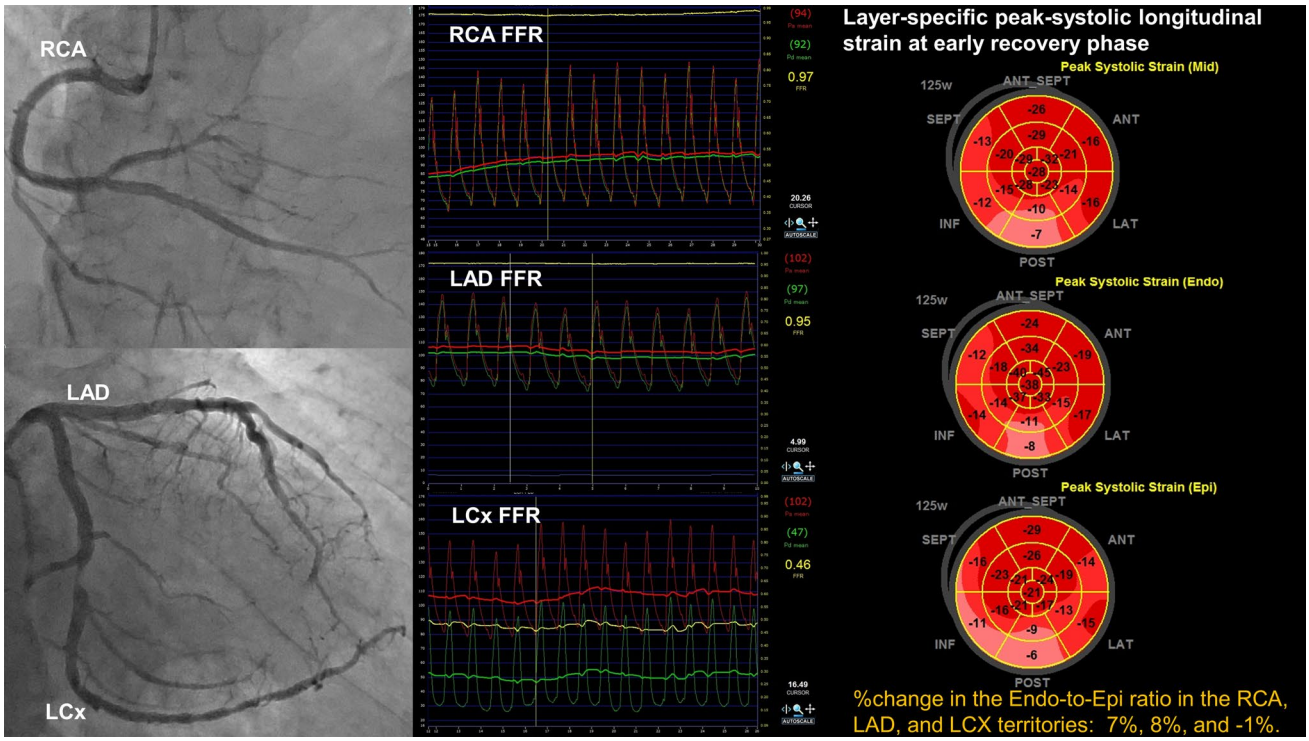

Fig. 1 Images form an 81-year-old male with effort angina pectoris referred for the evaluation of myocardial ischemia. On the speckle-tracking echocardiogram at early recovery phase post-exercise stress, the mid-, endocardial- (Endo), and epicardial-layer (Epi) longitudinal strain (LS) are impaired and percent change in the endocardial-to-epicardial LS ratio is attenuated in the posterior wall of the left ventricle. Coronary angiography reveals a significant stenosis in the left circumflex (LCX) with a fractional flow reserve (FFR) of 0.46, while no significant disease in the right coronary artery (RCA) and the left anterior descending coronary artery (LAD) without abnormal FFR

Invasive coronary angiography and fractional flow reserve

Invasive coronary angiography with 5-F or 6-F guiding catheters without side holes was performed using either the radial or femoral artery approach according to the standard protocol of the institute as described previously [21, 22]. At least two projections were obtained for each major coronary artery. FFR was measured with a 0.014-inch pressure monitoring guidewire (Volcano Inc., Rancho Cordova, CA, USA or St. Jude Medical, St. Paul, MN, USA) and was calculated by dividing mean distal coronary pressure by mean aortic pressure during maximal hyperemia induced by intracoronary papaverine (8 mg for the right coronary artery and 12 mg for the left coronary artery), intravenous adenosine (at 140 μg/kg/min), or intravenous adenosine 5′-triphosphate (at 140 μg/kg/min) [22, 23]. An FFR cutoff value of ≤ 0.80 was used to define the functional significance of CAD [1–4]. FFR measurement was attempted in 3 major epicardial coronary arteries unless chronic total occlusion (CTO) was present. For CTO lesions, a default FFR value of 0.50 can be applied as with previous studies [1–4, 23]. In all patients, intracoronary isosorbide dinitrate (at least 0.5 mg) was administered before coronary angiography and before FFR measurement. Quantitative coronary angiography (QCA) was performed off-line using validated software (QAngioXA version 7.1, Medis, Leiden, The Netherlands) by an experienced investigator, who was blind to the FFR values, the echocardiographic data, and clinical data. Lesion length, percent diameter stenosis (%DS), and minimal luminal diameter were measured in the end-diastolic angiographic image with an optimal projection showing minimal foreshortening of the lesion.

Reproducibility

Five and 10 studies were selected at random for the assessment of intra- and inter-observer reproducibility of the mid-, endocardial- and epicardial-layer LS measurements at baseline, at peak stress, at early and late recovery phase. To test intra-observer variability, a single observer analyzed the data twice. To test inter-observer variability, a second observer analyzed the data without the knowledge of the first observer's measurements.

Statistical analysis

The predefined primary analysis of this study was a comparison of the percent change of endocardial-layer LS from rest to exercise on a per-vessel basis. Based on a previous study [24], we estimated the percent change of the endocardial LS after stress as −7.2% in ischemic territories and + 4.2% in non-ischemic territories (the difference of the relative change: 11.7) and standard deviation (SD) of the relative change as 18.5%. On the basis of these assumptions, we estimated that 30 patients were required for a power of 80% and a 2-sided α level of 0.05, assuming the dropout rate of 5%.

Continuous variables were expressed as mean ± SD. Categorical variables were expressed as number (percentage). For analysis of multiple vessel territories per patient, generalized estimating equations were used to account for clustering effects. Logistic regressions were performed to evaluate if the parameters have predictive value for the detection of functionally significant CAD. Receiver operating characteristic (ROC) curves were produced to examine the diagnostic performance of the logistic regression models. The area under the ROC curve (AUC) was compared using a nonparametric approach proposed by DeLong et al. [25]. SPSS version 24 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) and R programming language version 3.1.4 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. A *P* value of less than 0.05 was considered to be statistically significant.

Results

We prospectively recruited 30 patients with stable CAD (Canadian Cardiovascular Society class of angina II or less) at Chiba University Hospital from December 2014 to June 2016. The baseline clinical, angiographic, and conventional TTE characteristics of the study population are shown in Tables 1, 2 and 3. Of the 88 vessels included in the analysis, FFR ≤ 0.80 was observed in 33 vessels, the mean invasive FFR value was 0.83 ± 0.16, and the mean percent diameter stenosis was 38.8 ± 19.6%. Systemic hemodynamic changes in response to exercise stress are shown in Table 4.

Layer-specific LS parameters in ischemic and non-ischemic territories

The worst regional mid-, endocardial-, and epicardial-layer peak systolic LS at early recovery phase was greater (i.e., more impaired) in the LV segments supplied by vessels with FFR ≤ 0.80 than in those with FFR > 0.80 (− 13.0 ± 4.4 vs. − 15.4 ± 5.2, *P* = 0.031; − 13.2 ± 4.5 vs. − 15.7 ± 5.1, *P* = 0.021; − 12.4 ± 4.0 vs. − 14.6 ± 5.1, *P* = 0.035, respectively) (Fig. 2). No significant differences were observed in the LS parameters at baseline, peak stress and late recovery phase between ischemic and non-ischemic territories. The lowest endocardial-to-epicardial ratio at peak stress, early recovery, late recovery phases was not significantly different between ischemia and non-ischemic territories (0.94 ± 0.16 vs. 0.98 ± 0.16, *P* = 0.27; 0.95 ± 0.16 vs. 1.00 ± 0.14, *P* = 0.16; 0.97 ± 0.13 vs. 0.96 ± 0.14, *P* = 0.74, respectively).

Table 1 Patient characteristics

Age (years)	69.4 ± 10.0
Male	24 (73%)
Coronary risk factors	
Hypertension	23 (70%)
Dyslipidemia	21 (64%)
Diabetes mellitus	10 (30%)
Current smoker	8 (24%)
Family history	4 (12%)
Medication	
Aspirin	33 (100%)
Thienopyridines	24 (73%)
ACE inhibitors or ARB	15 (46%)
β Blockers	10 (30%)
Statins	30 (91%)

Values are mean ± standard deviation, or *n* (%)

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CCS* Canadian cardiovascular society

Table 2 Conventional two-dimensional transthoracic echocardiographic findings

LV end-diastolic diameter (mm)	49.2 ± 4.9
LV end-systolic diameter (mm)	33.3 ± 9.8
Interventricular septum thickness in end diastole (mm)	9.5 ± 1.7
LV posterior wall thickness in end diastole (mm)	9.5 ± 1.2
Left atrial volume (ml)	35.3 ± 13.5
LV ejection fraction (Teicholtz) (%)	64.6 ± 5.8
LV end-diastolic volume (ml)	99.1 ± 20.3
LV end systolic volume (ml)	37.2 ± 11.0
LV ejection fraction (Simpson) (%)	62.9 ± 5.0
E (mitral early diastole velocity) (cm/s)	77.4 ± 22.1
A (mitral late diastolic peak velocity) (cm/s)	90.4 ± 20.2
E/*A*	0.9 ± 0.3
Deceleration time of the E-wave velocity (ms)	229.7 ± 38.6
E′ (peak mitral annular velocity during early diastole)	6.9 ± 1.6
E/*E*′	9.9 ± 3.4

Values are mean ± standard deviation

LV left ventricular

Table 3 Angiographic characteristics

	Overall	Ischemic territories (FFR ≤ 0.80)	Non-ischemic territories (FFR > 0.80)	*P* value
Fractional flow reserve	0.83 ± 0.16	0.66 ± 0.12	0.92 ± 0.07	< 0.001
QCA parameters				
Minimum lumen diameter (mm)	1.74 ± 0.80	1.1 ± 0.11	2.2 ± 0.08	< 0.001
Reference vessel diameter (mm)	2.84 ± 0.74	2.7 ± 0.68	3.0 ± 0.75	0.042
Percent diameter stenosis (%)	38.8 ± 19.6	55.5 ± 16.9	28.7 ± 13.6	< 0.001
Lesion length (mm)	10.7 ± 9.8	16.7 ± 13.2	7.0 ± 4.2	< 0.001

Values are mean ± standard deviation

QCA quantitative coronary angiography

Table 4 Exercise profile and hemodynamics

Exercise duration (min)	12.7 ± 3.4
Systolic blood pressure (mmHg)	
Rest	150 ± 17
Peak stress	185 ± 19
Early recovery	167 ± 21
Late recovery	140 ± 16
Heart rate (beats/min)	
Rest	67 ± 11
Peak stress	121 ± 17
Early recovery	92 ± 13
Late recovery	78 ± 13
Rate pressure product (mmHg/min)	
Rest	9560 ± 3134
Peak stress	21,238 ± 7187
Achieved exercise stage, *n* (%)	
25 W	1 (3.3%)
50 W	1 (3.3%)
75 W	9 (30.0%)
100 W	13 (43.3%)
125 W	6 (16.7%)
150 W	1 (3.3%)
Reason for exercise discontinuation	
Leg fatigue	12 (40.0%)
Achieved target heart rate	12 (40.0%)
Chest pain or dyspnea	5 (20%)

Values are mean ± standard deviation, or *n* (%)

The percent changes in the mid-, endocardial- and epicardial-layer LS from rest to early recovery phase were numerically lower in the ischemic territories than non-ischemic territories, which did not achieve a significant level (8.1 ± 20.9% vs. 15.5 ± 25.0%, $P = 0.12$; 10.4 ± 17.5% vs. 18.9 ± 24.2%, $P = 0.070$; 9.3 ± 18.7% vs. 14.2 ± 21.7%, $P = 0.27$, respectively). Neither the percent change in the endocardial-layer LS at peak stress (10.0 ± 19.3% vs. 16.5 ± 29.8%, $P = 0.24$) and late recovery phases (3.2 ± 19.2% vs. 7.3 ± 21.2%, $P = 0.29$) were significantly different between ischemic and non-ischemic territories. The percent change in the endocardial-to-epicardial ratio from baseline to peak stress, early recovery, and late recovery phases was significantly lower in the ischemic territories (FFR ≤ 0.80) compared with the non-ischemic territories (FFR > 0.80) (1.5 ± 11.2% vs. 6.6 ± 10.5%, $P = 0.009$; 2.8 ± 8.9% vs. 7.1 ± 12.6%, $P = 0.002$; 5.2 ± 8.8% vs. 8.5 ± 13.7%, $P = 0.026$, respectively) (Fig. 3).

Diagnostic performance of layer-specific LS parameters at early recovery phase and visual evaluation of LV wall motion on exercise stress echocardiography for the detection of ischemic territories

Based on ROC curve analyses for the detection of ischemic territories, the AUCs of the mid-, endocardial-, and epicardial-layer LS at early recovery phase and visual LV wall motion evaluation on exercise stress TTE are comparable (AUC = 0.621, 0.619, 0.616 and 0.618, $P = 0.99$). Likewise, modest diagnostic performance for the detection of ischemic territories was observed when using a single LS parameter at early recovery phase post exercise stress, including percent change in the mid-, endocardial- and, epicardial layer LS (AUC = 0.588, 0.606, and 0.571); the endocardial-to-epicardial LS ratio (AUC = 0.569); and percent change in the endocardial-to-epicardial LS ratio (AUC = 0.611). A combination of visual evaluation plus either the endocardial-layer LS, percent change in the endocarial-layer LS, or percent change in the endocardial-to-epicardial LS ratio at early recovery phase provided AUC of 0.712, 0.705, or 0.705 ($P = 0.053$, 0.073 or 0.074 vs. visual evaluation alone). A combination of the endocardial-layer LS and percent change in the endocardial-to-epicardial ratio at early recovery phase plus visual evaluation, and a combination of the endocardial-layer LS and percent change in the endocardial-layer LS at early

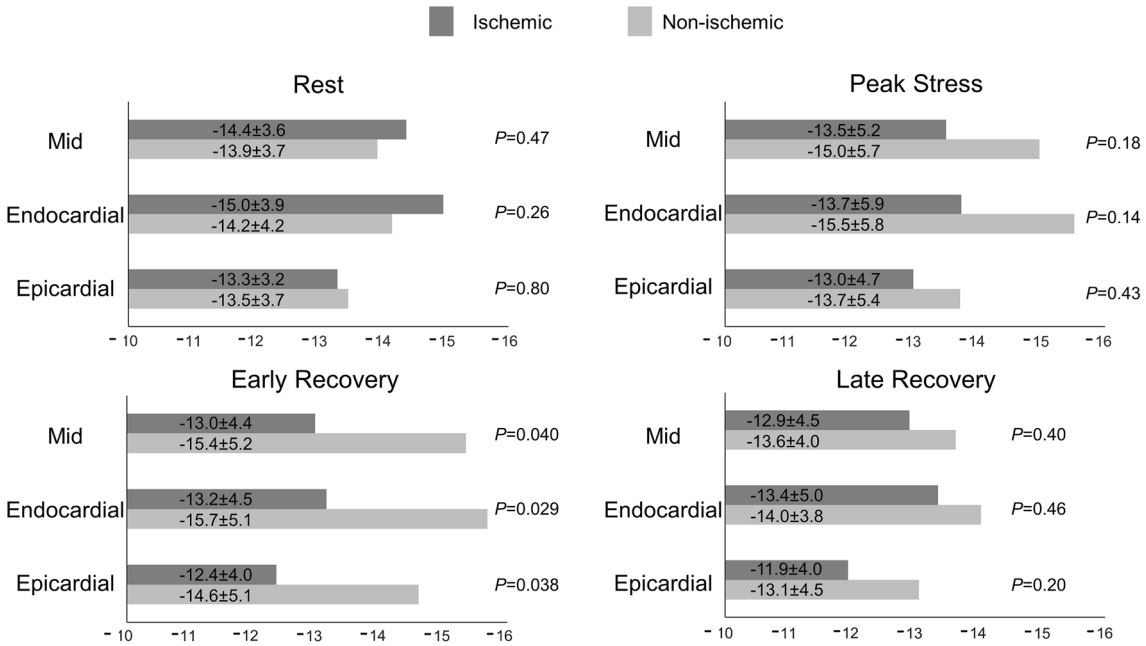

Fig. 2 Layer-specific longitudinal strain between ischemic vs. non-ischemic territories at rest, peak stress, early recovery, and late recovery phases

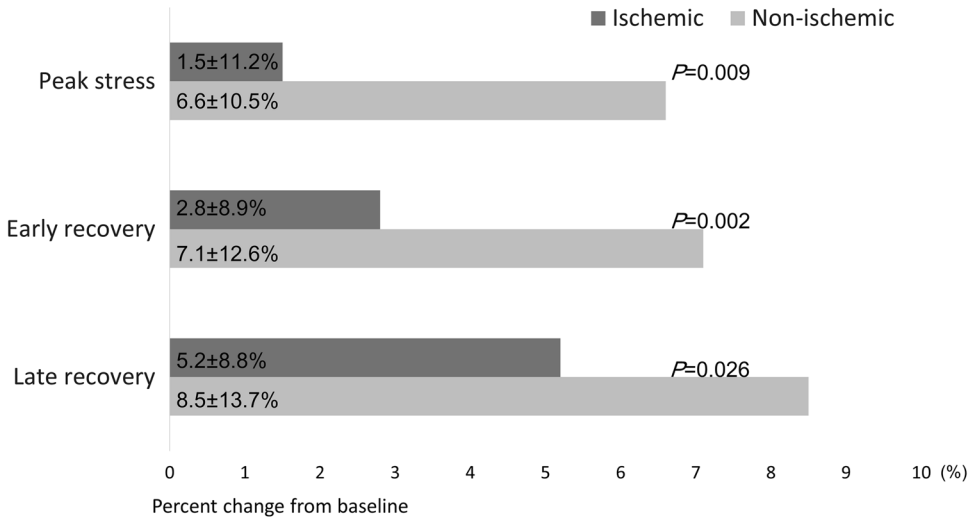

Fig. 3 Percent change in endocardial-to-epicardial longitudinal strain ratio between ischemic vs. non-ischemic territories from baseline to peak stress, early recovery, and late recovery phases

recovery phase plus visual evaluation provided a further improvement in AUC and better diagnostic performance than visual evaluation alone (AUC = 0.752 and 0.724, $P = 0.006$ and 0.028 vs. visual evaluation alone, respectively) (Fig. 4).

Intra- and inter-observer variability

For intra-observer variability, the intraclass correlation coefficients for the mid-, endocardial- and epicardial-layer LS measurements were 0.86, 0.91 and 0.75 at rest; 0.79, 0.83 and 0.72 at peak stress; 0.87, 0.91 and 0.80 at early recovery; and 0.91, 0.94 and 0.85 at late recovery, respectively. For interobserver variability, the corresponding interclass correlation coefficients were 0.84, 0.82 and 0.80 at rest; 0.73, 0.80 and 0.65 at peak stress; 0.71, 0.78 and 0.62 at early recovery; 0.79, 0.83 and 0.72 at late recovery, respectively.

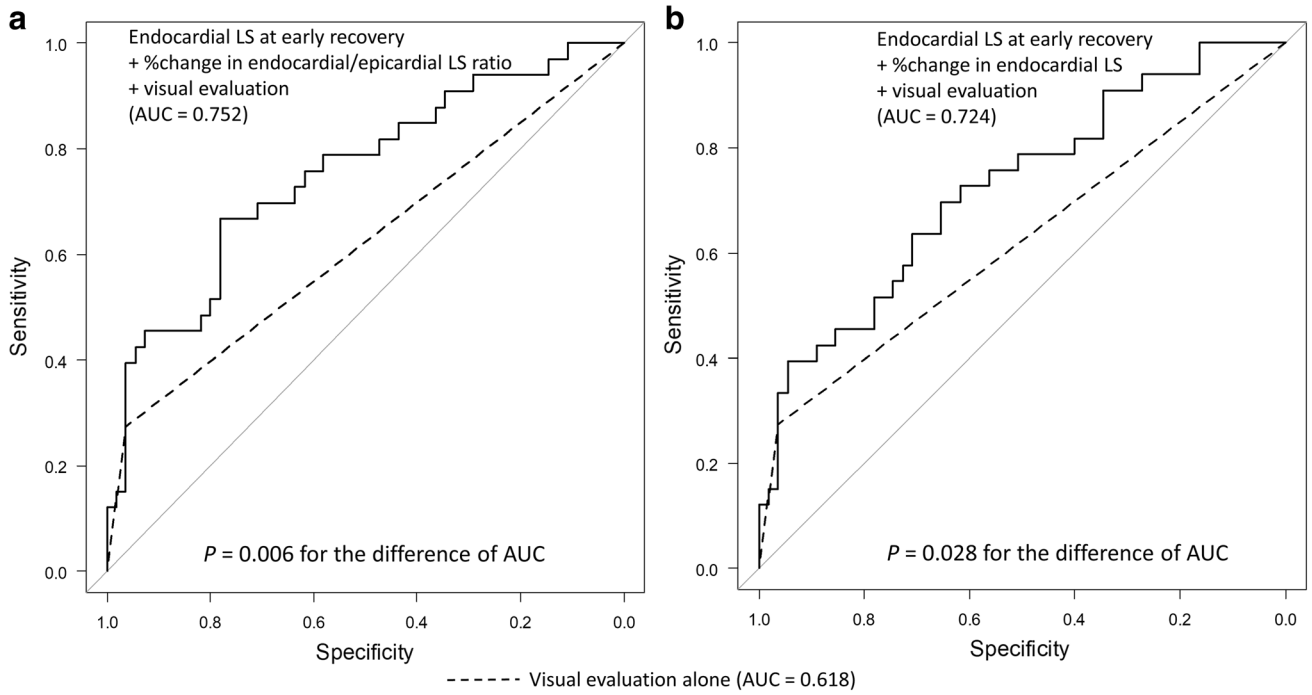

Fig. 4 Receiver operating characteristic curves for the detection of significant coronary artery disease. **a** A combination of endocardial longitudinal strain (LS) and percent change in endocardial-to-epicardial LS ratio at early recovery phase plus visual evaluation (a solid line in **a**) and **b** a combination of endocardial LS and percent change in endocardial-layer LS at early recovery phase plus visual evaluation (a solid line in **b**) produces a higher area under the curve compared with visual evaluation alone (a dashed line) (area under the curve (AUC): 0.752 (**a**) and 0.724 (**b**) vs. 0.618 (visual evaluation), $P = 0.006$ and 0.028)

Discussion

The present study evaluated layer-specific LS parameters on 2D speckle-tracking TTE with exercise stress in ischemic and non-ischemic territories as assessed by FFR. The main findings of the present study were that the layer-specific LS at early recovery phase after exercise stress and percent change in the endocardial-to-epicardial LS ratio from baseline to post-stress were significantly more impaired in the ischemic territories compared with the non-ischemic territories. The combination of endocardial LS at early recovery phase, percent change in the endocardial-to-epicardial LS ratio, and visual wall motion evaluation had incremental diagnostic value for the detection of ischemia compared with visual evaluation alone.

A few studies have investigated the diagnostic value of layer-specific strain on stress TTE for the detection of significant CAD [26, 27]. A retrospective study showed that endocardial-layer global LS during recovery after dobutamine stress was a sensitive parameter for CAD identification, and additional evaluation of endocardial global LS improved the diagnostic accuracy of dobutamine stress echocardiography (DSE) compared with standard DSE evaluation [26]. A prospective study evaluated layer-specific global strain during adenosine infusion and showed that change in layer-specific global LS from baseline to stress provided independent predictive value to the diagnosis of existing significant CAD when added to information given by patient characteristics and traditional echocardiographic parameters [27]. These studies support the application of layer-specific strain on stress TTE in line with the present study. However, they used pharmacological stress despite the fact that the guideline for stress echocardiography recommended exercise stress rather than pharmacologic stress for patients who are capable of performing an exercise test [28]. The present study extended the application of layer-specific LS to exercise stress TTE which we believe is the most physiological and first-line recommended non-invasive test for ischemia. In addition, both of the previous studies defined significant CAD based on anatomical severity of the coronary stenosis (e.g., > 70% luminal narrowing of a major epicardial coronary artery or > 50% luminal narrowing of the left main coronary artery), while the strength of the present study is that all patients had confirmation of the functional significance of coronary stenosis by invasive FFR measurement which is currently considered as invasive reference standard although several non-hyperemic or less-invasive approaches have been proposed [23, 29, 30]. This enabled comparison of LV wall deformation on TTE and the severity of ischemia at the vessel territory level.

The endocardial layer of the myocardium is more vulnerable to ischemia than the epicardial layer, and the endocardial-layer fibers are longitudinally oriented [16, 17]. Hence, theoretically, the endocardial-layer LS is more sensitive to detect ischemia. However, the previous studies did not demonstrate clear superiority of endocardial-layer strain over the other layers on stress TTE in the detection of significant CAD. In the present study, similar to the previous study [27], the AUCs for the detection of ischemic territories were not statistically different between the three layers although the difference in LS values between the ischemic and non-ischemic territories was more prominent numerically in the epicardial layer. The new finding from the present study is that the endocardial-to-epicardial LS ratio, assessed as an indicator of endocardial-layer dependency of the LV myocardium, increased after exercise stress in the non-ischemic myocardium by average 6.6%, 7.1% and 8.5% from baseline at peak stress, early recovery and late phases, while such augmentation was attenuated in the ischemic myocardium. In addition, a combination of the endocardial LS and percent change in the endocardial-to-epicardial LS ratio at early recovery phase plus visual wall motion evaluation had incremental diagnostic value for the detection of ischemic territory; this combination provided the numerically highest AUC value although a combination of the endocardial LS and percent change in the endocardial LS plus visual evaluation also had incremental diagnostic value as well. These results indicate that the evaluation of change in the endocardial-to-epicardial LS ratio in addition to mere LS value on stress TTE would be a possible utility of layer-specific strain analysis for the assessment of myocardial ischemia. We need to further evaluate whether the diagnostic advantage of the evaluation of the endocardial-to-epicardial ratio overweighs the simplicity of evaluating just LS value or change in LS value post stress in the clinical setting.

The significant differences in the multi-layer LS parameters between the ischemic and non-ischemic territories were observed only at early recovery phase after exercise stress in the present study. This result is in line with previous studies using dobutamine stress TTE [12, 26]. At peak stress, it may be difficult to acquire adequate image quality for the speckle-tracking strain analysis because of higher heart rates associated with strenuous movement of the heart. During the early recovery phase, lower heart rate compared with at peak stress might provide successful speckle tracking in the state that ischemia-derived abnormalities in LV wall motion persist. Furthermore, LS parameters at early recovery phase had better reproducibility than those at peak stress. Therefore, when applying multi-layer LS on stress TTE to the detection of myocardial ischemia, an early recovery phase appeared to be the most appropriate timing for the evaluation.

Study limitation

There were some limitations to the present study. First, our study population was small and located in a single center. Second, 18 patients could not achieve their target heart rates during the exercise stress tests. However, they achieved the mean of 86% of the target heart rates and all but 2 of them achieved more than 80% of the target heart rates. Third, we were unable to completely assign all myocardial segments to the appropriate coronary perfusion territories. Finally, we could not establish a diagnostic algorithm for the diagnosis of myocardial ischemia using the layer-specific strain on stress TTE from the present study. The algorithm should be made based on and validated in studies with a larger sample size.

Conclusions

The results of the present study suggested that assessing layer-specific LS and the endocardial-to-epicardial LS ratio after exercise stress on speckle-tracking TTE may have potential for objective and quantitative evaluation for the assessment of myocardial ischemia. Further studies in a larger population are needed to confirm these findings.

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Compliance with ethical standards

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

References

1. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, FAME Study Investigators (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 360:213–224
2. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF, FAME 2 Trial Investigators (2012) Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 367:991–1001
3. Nishi T, Piroth Z, De Bruyne B, Jagic N, Möbius-Winkler S, Kobayashi Y, Derimay F, Fournier S, Barbato E, Tonino P, Jüni P, Pijls NHJ, Fearon WF (2018) Fractional flow reserve and quality-of-life improvement after percutaneous coronary intervention in patients with stable coronary artery disease. Circulation 138:1797–1804

4. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, Jüni P, Pijls NHJ, Hlatky MA, FAME 2 Trial Investigators (2018) Clinical outcomes and cost-effectiveness of fractional flow reserve-guided percutaneous coronary intervention in patients with stable coronary artery disease: three-year follow-up of the FAME 2 trial (fractional flow reserve versus angiography for multivessel evaluation). Circulation 137:480–487
5. Hoit BD (2011) Strain and strain rate echocardiography and coronary artery disease. Circ Cardiovasc Imaging 4:179–190
6. Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, Abraham TP, Belohlavek M (2005) Two-dimensional strain—a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. J Am Soc Echocardiogr 18:1247–1253
7. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, Støylen A, Ihlen H, Lima JA, Smiseth OA, Slørdahl SA (2006) Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 47:789–793
8. Delgado V, Mollema SA, Ypenburg C, Tops LF, van der Wall EE, Schalij MJ, Bax JJ (2008) Relation between global left ventricular longitudinal strain assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. J Am Soc Echocardiogr 21:1244–1250
9. Hanekom L, Cho GY, Leano R, Jeffriess L, Marwick TH (2007) Comparison of two-dimensional speckle and tissue Doppler strain measurement during dobutamine stress echocardiography: an angiographic correlation. Eur Heart J 28:1765–1772
10. Ng AC, Sitges M, Pham PN, da Tran T, Delgado V, Bertini M, Nucifora G, Vidaic J, Allman C, Holman ER, Bax JJ, Leung DY (2009) 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 158:836–844
11. Joyce E, Hoogslag GE, Al Amri I, Debonnaire P, Katsanos S, Bax JJ, Delgado V, Marsan NA (2015) 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 28:1379–1389.e1
12. Uusitalo V, Luotolahti M, Pietilä M, Wendelin-Saarenhovi M, Hartiala J, Saraste M, Knuuti J, Saraste A (2016) Two-dimensional speckle-tracking during dobutamine stress echocardiography in the detection of myocardial ischemia in patients with suspected coronary artery disease. J Am Soc Echocardiogr 29:470–479.e3
13. Aggeli C, Lagoudakou S, Felekos I, Panagopoulou V, Kastellanos S, Toutouzas K, Roussakis G, Tousoulis D (2015) Two-dimensional speckle tracking for the assessment of coronary artery disease during dobutamine stress echo: clinical tool or merely research method. Cardiovasc Ultrasound 13:43
14. Reant P, Labrousse L, Lafitte S, Bordachar P, Pillois X, Tariosse L, Bonoron-Adele S, Padois P, Deville C, Roudaut R, Dos Santos P (2008) Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. J Am Coll Cardiol 51:149–157
15. Adamu U, Schmitz F, Becker M, Kelm M, Hoffmann R (2009) Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters. Eur J Echocardiogr 10:303–308
16. Oh BH, Volpini M, Kambayashi M, Murata K, Rockman HA, Kassab GS, Ross J Jr (1992) Myocardial function and transmural blood flow during coronary venous retroperfusion in pigs. Circulation 86:1265–1279
17. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB (1977) The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 56:786–794
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography (2005) 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 18:1440–1463
19. Nishi T, Funabashi N, Ozawa K, Takahara M, Fujimoto Y, Kamata T, Kobayashi Y (2016) Resting multilayer 2D speckle-tracking transthoracic echocardiography for the detection of clinically stable myocardial ischemic segments confirmed by invasive fractional flow reserve. Part 1: vessel-by-vessel analysis. Int J Cardiol 218:324–332
20. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS, American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging (2002) 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 105:539–542
21. Nishi T, Kitahara H, Fujimoto Y, Nakayama T, Nagashima K, Hanaoka H, Kobayashi Y (2018) Intravenous nicorandil versus adenosine for fractional flow reserve measurement: a crossover, randomized study. Heart Vessels 33:1570–1575
22. Nishi T, Kitahara H, Iwata Y, Fujimoto Y, Nakayama T, Takahara M, Sugimoto K, Kobayashi Y (2016) Efficacy of combined administration of intracoronary papaverine plus intravenous adenosine 5′-triphosphate in assessment of fractional flow reserve. J Cardiol 68:512–516
23. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B, Bezerra H, Osawa K, Marwan M, Naber C, Erglis A, Park SJ, Christiansen EH, Kaltoft A, Lassen JF, Bøtker HE, Achenbach S, NXT Trial Study Group (2014) Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 63:1145–1155
24. Hwang HJ, Lee HM, Yang IH, Lee JL, Pak HY, Park CB, Jin ES, Cho JM, Kim CJ, Sohn IS (2014) The value of assessing myocardial deformation at recovery after dobutamine stress echocardiography. J Cardiovasc Ultrasound 22:127–133
25. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44:837–845
26. Park JH, Woo JS, Ju S, Jung SW, Lee I, Kim JB, Kim SJ, Kim W, Kim WS, Kim KS (2016) Layer-specific analysis of dobutamine stress echocardiography for the evaluation of coronary artery disease. Medicine (Baltimore) 95:e4549
27. Ejlersen JA, Poulsen SH, Mortensen J, May O (2017) Diagnostic value of layer-specific global longitudinal strain during

adenosine stress in patients suspected of coronary artery disease. Int J Cardiovasc Imaging 33:473–480
28. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of Echocardiography (2007) American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 20:1021–1041
29. Nishi T, Johnson NP, De Bruyne B, Berry C, Gould KL, Jeremias A, Oldroyd KG, Kobayashi Y, Choi DH, Pijls NHJ, Fearon WF, CONTRAST Study Investigators (2017) Influence of contrast media dose and osmolality on the diagnostic performance of contrast fractional flow reserve. Circ Cardiovasc Interv. https://doi.org/10.1161/CIRCINTERVENTIONS.117.004985
30. Nishi T, Fearon WF (2018) Fractional flow reserve derived from routine coronary angiography. Int J Cardiol 271:51–52