Chapter Nine

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

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ABSTRACT

Objectives

Residual ischemia detection after ST-segment elevation myocardial infarction (STEMI) during dobutamine stress echocardiography (DSE) using visual analysis is challenging. The current study aimed to investigate feasibility and accuracy of 2-dimensional speckle-tracking (2DSTE) strain DSE to detect significant coronary artery disease (CAD) after STEMI.

Methods and Results

First STEMI patients (n=105, 60±11 years, 86% male) treated with primary percutaneous coronary intervention, undergoing full-protocol DSE at 3 months and repeat coronary angiography within 1 year were retrospectively included. Using 2DSTE, segmental and global left ventricular (LV) peak longitudinal systolic strain (PLSS) at rest and peak stress and change (Δ) in PLSS were measured. Significant CAD was defined as detection of >70% diameter stenosis at coronary angiography. A total of 1,653 segments (93%) and 1,645 (92%) were analysable at rest and peak, respectively. At follow-up, 38 patients (36%) showed significant angiographic CAD. These patients demonstrated a greater worsening in global PLSS from rest to peak (-16.8±0.5% to -12.6±0.5%) compared to patients without significant CAD (-16.6±0.4% to -14.3±0.3%; group stage interaction p<0.001). Optimal cut-off of ΔPLSS for detection of significant CAD on ROC curve analysis was ≥1.9% (AUC 0.70, sensitivity 87%, specificity 46%, accuracy 60%). Using a sentinel segment approach (apex, mid posterior and mid inferior for left anterior descending artery, left circumflex and right coronary artery territories, respectively), larger segmental ΔPLSS was also independently associated with significant CAD (OR1.1, 95% CI 1.1-1.2).

Conclusions

2DSTE strain analysis is feasible on DSE after STEMI and represents a promising new technique to detect significant angiographic CAD at follow-up.

INTRODUCTION

Patients who recover from ST-segment elevation myocardial infarction (STEMI) remain at high risk for new ischemic events and premature death.[1] For optimal risk stratification in post-STEMI patients, the recently updated European Society of Cardiology guidelines include stress testing or imaging, such as dobutamine stress echocardiography (DSE), in patients with multivessel disease or in whom revascularization of other vessels is being considered as a class IA recommendation.[2] DSE is frequently used for the detection, localization and assessment of extent of ischemia in patients with suspected or established coronary artery disease (CAD) due to its wide availability, low-cost and lack of ionizing radiation.[3] However, assessment of regional myocardial function on DSE relies on semi-quantitative evaluation of endocardial excursion and wall thickening and is therefore highly subjective and image quality dependent, even in the hands of expert observers.[4,5] Moreover, detection of residual and/or new ischemia during DSE after STEMI is particularly challenging due to the presence of existing wall motion abnormalities.

The need for more quantitative techniques to objectively evaluate regional left ventricular (LV) myocardial performance during DSE has led to the incorporation of deformation indices such as 2-dimensional (2D) speckle-tracking (STE) derived longitudinal strain, a highly sensitive alternative method of quantifying regional myocardial function based on gray-scale ultrasound imaging. Several experimental studies have already validated 2D strain techniques against sonomicrometry during dobutamine infusion and/or ischemia.[6-9] Recently, clinical studies have investigated the diagnostic value of 2D strain and related parameters during DSE for inducible ischemia detection in patients with suspected CAD.[10-13] However, despite the known prognostic value of residual ischemia detection in this population, few clinical studies have investigated 2DSTE derived strain parameters on DSE after STEMI.[14,15]

The present study hypothesized that 2DSTE may be incremental to conventional visual analysis in characterizing the complex ischemic substrate(s) in patients with previous STEMI. Therefore, the aim was to compare the feasibility and accuracy of both wall motion score (WMS) and 2DSTE strain and its derived parameters on DSE after STEMI for the detection of angiographically significant CAD at follow-up.

METHODS

Patient population

All first STEMI patients presenting to our institution between November 2010 and February 2012 and treated according to the MISSION! protocol were evaluated for inclusion in this retrospective study. This protocol is designed to improve care around all aspects of STEMI and is based on the most recent American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines.[2,16,17] Diagnosis of acute myocardial infarction was made on the basis of typical electrocardiographic changes and/or ischemic chest pain associated with elevation of cardiac enzymes.[18] DSE is also performed as part of this

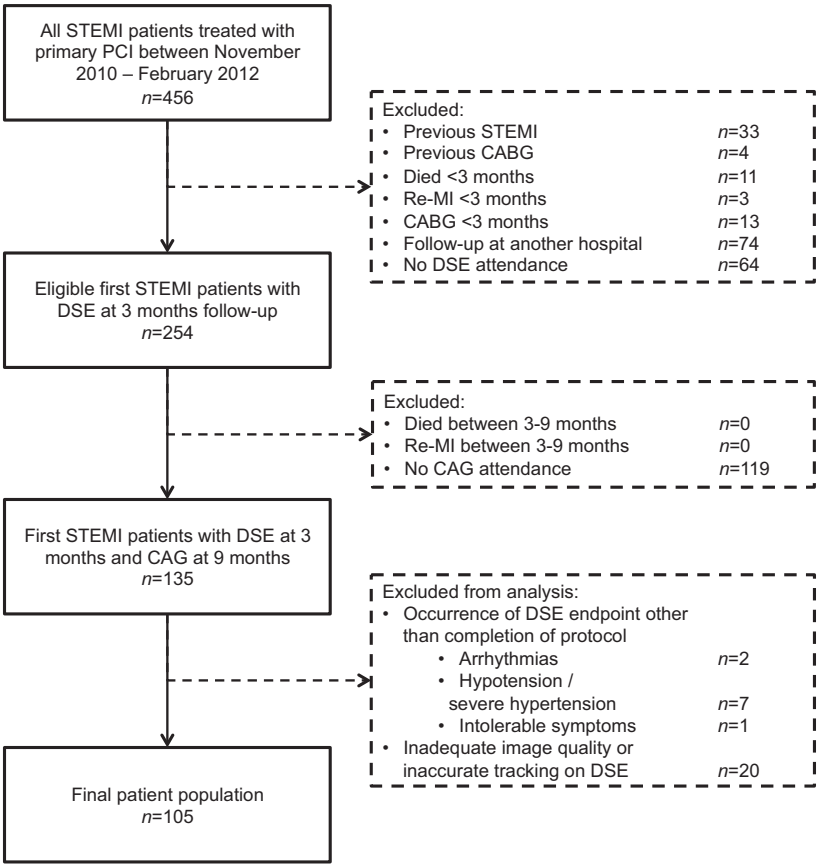

Figure 1. CONSORT diagram of the patient population.
CABG, coronary artery bypass grafting; CAG, coronary angiography; DSE, dobutamine stress echocardiography; PCI, percutaneous coronary intervention; Re-MI, repeat myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

protocol 3 months after STEMI in all patients for risk stratification and to optimize management through detection of new or residual ischemia and/or determination of myocardial viability.[14,19,20] Repeat coronary angiography is performed during follow-up as part of this protocol if ischemia is demonstrated on DSE and/or if patients present with symptoms and signs suggestive of ischemia, as clinically appropriate.

For inclusion in the study, patients were required to have undergone both full-protocol DSE as recommended by our insitutional guideline and repeat coronary angiography (clinically and/or DSE-driven) within 1 year. Patients were excluded from the study if they had undergone coronary artery bypass grafting or suffered a repeat myocardial infarction up to the date of repeat coronary angiography. Additionally, patients were excluded if they reached an endpoint other than completion of the DSE protocol[21] (see below) or if image quality at any DSE stage was suboptimal for 2DSTE analysis (Figure 1).

Patient data was prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, the Netherlands) and retrospectively analyzed. For this retrospective analysis of clinically acquired data, the Institutional Review Board waived the need for patient written informed consent.

Dobutamine Stress Echocardiography

DSE was performed according to a standard protocol.[21] The decision on whether to instruct patients to continue or suspend beta-blocker therapy 48 hours prior to the study was clinically directed. After a baseline electrocardiogram (ECG) and echocardiogram were recorded, dobutamine was administered beginning at a dose of 5ug kg/min. The dose was increased at 3-minute intervals up to 40ug/kg/min and if target heart rate (85% of age-predicted maximal heart rate) was not achieved following this, intravenous atropine in divided doses of 0.25 to 0.5mg (up to 2mg) was given. Endpoints of our DSE protocol were completion of the test, significant arrhythmias, hypotension, severe hypertension (systolic BP >240mm/Hg) or intolerable symptoms. Stress echocardiogram images were obtained using a commercially available ultrasound system (iE33, Philips Medical Systems, Bothell, Washington, USA) equipped with a broadband S5-1 transducer with the patient in the left lateral decubitus position and were acquired from apical (4-, 2- and 3-chamber) views at rest, low-dose and peak stress phases of dobutamine. Two-dimensional gray-scale images were obtained at a frame rate ranging from 60-100 frames per second for all stages. Images were saved in cine-loop format from 3 consecutive beats and analysis was subsequently performed offline using Q-Lab Version 9.0 (Philips Medical Systems). Low-dose images were acquired at 20ug/

kg/min; peak stress images were acquired upon achievement of target heart rate. Development of ischemia was defined by conventional visual analysis as a new or worsening wall motion abnormality, or, in the case of segments with pre-existing wall motion abnormalities, as a biphasic response if there was augmentation at low-dose followed by further deterioration at peak stress.[21]

Conventional DSE analysis

Wall motion was independently assessed by an experienced observer blinded to the coronary angiography results according to the 17-segment model of the American Society of Echocardiography.[22] Each segment was scored individually based on its motion and systolic thickening (1=normal; 2=hypokinesia; 3=akinesia; 4=dyskinesia). Global WMS index (WMSI) was then calculated for each patient as the sum of the segment scores divided by the number of segments scored.[22] Change in WMSI from rest to peak was also assessed (ΔWMSI).

2DSTE strain analysis

Quantitative strain analysis using 2DSTE was performed independently to conventional visual analysis by experienced observers blinded to the coronary angiography results. In particular, longitudinal strain was measured for each LV segment using the apical 4-, 2- and 3-chamber views. The LV endocardial border was traced using the optimal frame for endocardial identification in all 3 apical views and the automatically created region of interest was manually adjusted to the thickness of the myocardium. Segments were discarded if tracking was of persistent poor quality following readjustment of the region of interest. Subsequently, numerical and graphical displays of deformation parameters were automatically generated for all LV segments.[23] Aortic valve closure was defined in the apical long-axis view and the interval between the R wave and this time point was then automatically measured to serve as a reference for identification of end-systole.

LV peak longitudinal systolic strain (PLSS) was measured for each segment as maximal longitudinal shortening in systole. The presence of further segmental shortening occurring in diastole beyond maximal systolic shortening – post-systolic shortening (PSS) – and its magnitude (peak shortening in diastole minus PLSS) was assessed.[24] Post-systolic shortening index (PSI) was then calculated as PSS divided by maximum shortening expressed as a percentage for those segments with PSS present.[24] The magnitude of change in each parameter between stages (peak-rest) was also calculated (ΔPLSS, ΔPSS, ΔPSI). Notably, longitudinal shortening is denoted by convention using a negative sign; therefore, a positive value of ΔPLSS indicates more impaired global PLSS from rest to peak. For all 3 parameters, global values were also obtained by averaging the original segmental data.

Coronary angiography

All patients underwent selective coronary angiography using the Judkins technique and images were read by an experienced interventionalist. Significant CAD was defined as >70% luminal diameter stenosis in ≥1 of the 3 major epicardial vessels, as assessed by computer-assisted quantitative coronary angiography using multiple planes. Segments were assigned to a specific coronary territory based on a standardized perfusion model: left anterior descending (LAD) (basal and mid anteroseptal, basal and mid anterior, apical anterior and septal and the apex), left circumflex (LCx) (basal and mid posterior and all lateral segments) and right coronary artery (RCA) (basal and mid septal and all inferior segments).[23]

Statistical analysis

Continuous variables are presented as mean ± standard deviation or standard error or as median and interquartile range as appropriate. Categorical data are presented as absolute numbers and percentages.

For global (per patient) analysis, Student's paired *t*-test was firstly performed to assess differences across stages for individual DSE parameters in the total population. Subsequently, a linear mixed-effects modeling approach was used to compare differences in conventional DSE (WMSI, heart rate and blood pressure) and 2DSTE (PLSS, number of segments with PSS and PSI) parameters between patients with or without significant CAD across both stages (group-stage interaction). Differences within groups at each stage were also evaluated. Subsequently, the relationship between the presence of significant CAD at follow-up angiography and a range of putative predictor variables (clinical, conventional DSE and 2DSTE parameters) was evaluated using univariate and multivariate logistic regression analysis. Candidate variables associated with a p-value <0.05 on univariate analysis were included in the multivariate analysis. Because of multicollinearity, individual conventional DSE and quantitative 2DSTE parameters achieving this significance level were entered into separate multivariate models together with the other "fixed" clinical parameters achieving univariate significance at this same level. Thereafter, receiver operating characteristics (ROC) curve analysis was performed for the 2DSTE parameter achieving the strongest independent significance on multivariate analysis (ΔPLSS) to evaluate their predictive ability for the presence of significant CAD. Sensitivities, specificities and diagnostic accuracies were calculated using cut-off values based on the principle of optimal sensitivity (with reasonable specificity) for the detection of significant CAD at follow-up. Finally the likelihood ratio test was performed to evaluate the incremental value of quantitative strain analysis (using this cut-off) over conventional visual analysis (using the cut-off of ≥2 stress-induced wall

motion abnormalities[25]) and clinical parameters for the prediction of significant follow-up CAD.

For segmental analysis, ROC curves were performed to investigate the accuracy of ΔPLSS across each segment for the detection of a significant stenosis (>70%) in the corresponding territory. For further segmental analysis involving WMS, all segments were included in the analyses. In contrast, in order to facilitate increased feasibility of 2D strain assessment on DSE technique for routine clinical use, representative segments ("sentinel segments") were chosen for further analysis, selected as segments displaying the highest area under the curve (AUC) on ROC curve analysis for the detection of a significant stenosis (>70%) in the corresponding territory. Sensitivities, specificities and accuracies were also calculated for each sentinel segment for the detection of significant CAD in that territory using the cut-off previously derived at global level. Generalized estimating equations (allowing adjustment for the fact that segments in each patient are correlated) were then used to test the association between segmental parameters and the presence of a significant stenosis in the corresponding coronary territory (both unadjusted and adjusted for significant clinical parameters at that level). Finally, subgroup analyses were performed using these sentinel segments for the risk of >70% stenosis in the corresponding territory among relevant clinical (age, gender, diabetes) and infarct (infarct-related artery [IRA], single or multivessel disease, LAD or not territory, peak troponin T level according to median) subgroups.

All statistical tests were 2-sided and a p-value of <0.05 was considered statistically significant. The statistical software program SPSS (version 20.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

Reproducibility

Reproducibility of PLSS was assessed at both global and segmental level at both stages of DSE and expressed as both interclass correlation coefficients and as a percentage of the absolute difference divided by the mean of the pair-repeated observations (absolute difference). For global intra- and inter-observer variability, 10 patients (total 340 segments) were selected at random and measurements were repeated by the same observer on the same echocardiographic images at least 2 weeks apart and by another independent observer. Similarly, intra- and inter-observer variability was calculated for each sentinel segment (total 60 segments).

RESULTS

Patient Population

Of 135 first STEMI patients meeting initial inclusion criteria, 7% (n=10) were excluded due to occurrence of a DSE endpoint other than completion of the protocol (Figure 1). A further 15% (n=20) were excluded due to either inadequate image quality at rest or peak-dose or inaccurate tracking involving a full regional wall or >2 segments within the same coronary territory. Clinical characteristics of the remaining 105 patients (mean age 60±11 years, 86% male) at the time of admission for STEMI are shown in Table 1. The LAD artery was the IRA in 33% of patients and just over 50% of the patient population had multivessel disease (defined as angiographic stenosis ≥50% in ≥2 vessels, including the IRA).

Median time from DSE to follow-up coronary angiography was 6 (interquartile range 5, 6) months. In total, 36% of patients (n=38) had significant CAD >70% in ≥1 epicardial vessel at follow-up (LAD 26%, LCx 11%, RCA 14%). There were no

Table 1. Clinical characteristics of the patient population at the time of admission for STEMI

	Total patient population (n=105)
Age (years)	60 ± 11
Male gender, n (%)	90 (86%)
Current or previous smoking, n (%)	60 (57%)
Diabetes, n (%)	9 (9%)
Family history of CAD, n (%)	41 (39%)
Hyperlipidemia, n (%)	23 (22%)
Hypertension, n (%)	38 (36%)
Killip class ≥2, n (%)	4 (4%)
Infarct-related artery, n (%)	
Left anterior descending	35 (33%)
Left circumflex	24 (23%)
Right coronary artery	46 (44%)
Multivessel disease, n (%)	59 (56%)
Final TIMI flow ≥2, n (%)	103 (98%)
Peak CPK level (U/L)	1,478 (661, 2,611)
Peak TnT level (μg/L)	3.3 (1.2, 6.3)
Dual antiplatelet therapy, n (%)	103 (98%)
ACE inhibitors/ARBs, n (%)	101 (96%)
Beta-blockers, n (%)	99 (94%)
Statins, n (%)	105 (100%)

ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CPK, creatinine phosphokinase; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; TnT, cardiac troponin T; WMSI, wall motion score index.

differences in dual antiplatelet (97% vs. 99%, p=0.68), statin (100% vs. 100%, p=1.0), angiotensin converting enzyme inhibitor/angiotensin receptor blocker (95% vs. 97%, p=0.56) or beta-blocker therapy (95% vs. 94%, p=0.88) at time of discharge after STEMI between those with significant CAD at follow-up angiography compared to those without significant CAD.

Conventional DSE analysis

The majority of patients (55%, n=76) had suspended beta-blocker therapy prior to DSE. Mean heart rates at rest and peak-dose were 66±13 and 138±13 beats per minute, respectively (p<0.001). In total, WMS assessment was feasible in 1,784 (100%), 1,768 (99%) and 1,785 (100%) segments at rest, low-dose and

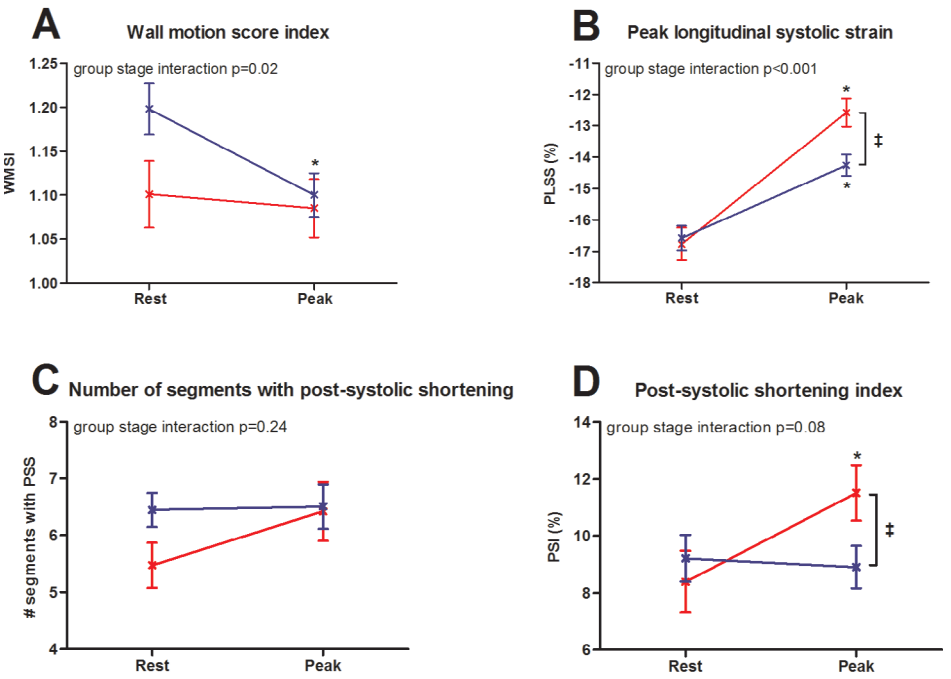

Figure 2. Conventional dobutamine stress echocardiography analysis (WMSI) and 2D speckle tracking echocardiography strain analysis (PLSS, PSI and number of segments with PSS) compared across patients with significant CAD (red line) or without significant CAD (blue line) at follow-up. Group stage interaction p-values (differences in parameters between groups across both stages) are shown. * p-value <0.05 compared to rest stage. ‡ p-value <0.05 between patients with or without significant CAD at this particular stage. Data are presented as mean ± standard error.
2D, 2-dimensional; PLSS, peak longitudinal systolic strain; PSI, post-systolic shortening index; PSS; post-systolic shortening; WMSI, wall motion score index.

peak stress, respectively. The majority (52%, n=55) of patients had an abnormal WMSI at rest, consisting of 220 (12%) abnormal segments. Stress-induced wall motion abnormalities were seen in 11% of patients (n=51 segments). A biphasic response was observed in 9 (0.5%) segments. Mean WMSI at rest and peak-dose were 1.16±0.24 and 1.09±0.20, respectively (p<0.001 for change).

Dividing the patient population according to patients with or without significant CAD at follow-up, the increase in heart rate (p=0.43), systolic (p=0.75) and diastolic (p=0.59) blood pressure between groups from rest to peak and at each stage was similar (Supplemental Figure 1). The change in WMSI during DSE was significantly different from rest to peak stress between patients with and without significant CAD at follow-up (group-stage interaction p=0.02, Figure 2). Within group analysis showed a significant decrease in WMSI throughout DSE in patients without significant CAD (1.20±0.03 to 1.10±0.03, p<0.001), and no significant change in WMSI (1.10±0.04 to 1.09±0.03, p=0.63) from rest to peak stress in those with significant CAD at follow-up.

Quantitative 2DSTE analysis

Mean frame rates at rest and peak stress were 71±12 and 71±11 frames per second, respectively. In total, 1,653 (93%) and 1,645 (92%) segments were analysable at rest and at peak stage, respectively. Least feasible segment was the mid anterior (82%) at rest and the mid anteroseptal segment (76%) at peak stress (Table 3). In the total population, mean global PLSS decreased significantly from -16.6±3.2% at rest to -13.6±2.9% at peak-dose (p<0.001) while both mean global number of segments with PSS (6.1±2.5 to 6.5±3.2, p=0.29) and global PSI (8.9±6.7% to 9.9±6.1%, p=0.33) showed a non-significant trend towards increase.

Differences in 2DSTE global parameters between patients with or without significant CAD across stages and groups are also illustrated in Figure 2. The only parameter to exhibit a significant group-stage interaction was global PLSS (significant CAD: -16.8±0.5% to -12.6±0.5%; no significant CAD: -16.6±0.4% to -14.3±0.3%, p<0.001). Although global PSI only showed a trend towards overall group-stage significance (p=0.08), it did increase significantly from rest to peak in the patients with significant CAD (8.4±1.1% to 11.5±1.0%, p=0.02), leading to a significant difference at peak-stage between the 2 groups (11.5±1.0% vs. 8.9±0.7%, p=0.04).

Conventional Vs. Quantitative DSE Analysis: Global Assessment

Table 2 shows the results of univariate and multivariate analyses of global conventional and 2DSTE parameters on DSE associated with >70% stenosis in ≥1 epicardial vessel at follow-up post-STEMI. While ΔWMSI was associated with significant CAD at univariate level (odds ratio [OR] 38, 95% CI 1.2-1,178, p=0.04),

after adjusting for clinical parameters, no independent association was demonstrated (OR 14, 95% CI 0.32-643, p=0.17). Both peak PLSS (OR 1.2, 95% CI 1.0-1.5, p=0.03) and a larger positive value of global ΔPLSS (representing greater impairment of global PLSS from rest to peak) (OR 1.3, 95% CI 1.1-1.6, p=0.01) were the only DSE (and 2DSTE strain) parameters independently associated with significant CAD on multivariate analysis (Table 2). Given the greater strength of the association for ΔPLSS, this parameter was chosen as the primary 2DSTE strain parameter to perform further analyses. Of note, for this multivariate model, age (OR 1.0, 95% CI 1.0-1.1, p=0.03) and multivessel disease (OR 4.0, 95% CI 1.4-11, p=0.009) were also independent predictors of significant CAD at follow-up.

On ROC curve analysis, the optimal cut-off of global ΔPLSS for detection of significant CAD at follow-up was ≥1.9% (AUC 0.70, p=0.001); sensitivity, specificity and diagnostic accuracy were 87%, 46% and 60%, respectively. Comparison diagnostic statistics for WMS analysis, using the cut-off of ≥2 stress-induced new or worsening wall motion abnormalities, were 11%, 94% and 64% for sensitivity, specificity and diagnostic accuracy respectively.

Table 2. Global conventional and speckle-tracking echocardiography strain parameters on dobutamine stress echocardiography associated with the identification of a >70% stenosis in ≥1 epicardial vessel on coronary angiography

	Univariate analysis		**Multivariate analysis ***	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Rest WMSI	0.12 (0.01-1.0)	0.05		
Peak WMSI	0.69 (0.09-5.2)	0.72		
ΔWMSI	38 (1.2-1,178)	0.04	14 (0.32-643)	0.17
Rest PLSS (%)	0.98 (0.87-1.1)	0.76		
Peak PLSS (%) **	**1.3 (1.1-1.5)**	**0.006**	**1.2 (1.0-1.5)**	**0.03**
ΔPLSS (%) ***	**1.4 (1.1-1.6)**	**0.001**	**1.3 (1.1 to 1.6)**	**0.01**
Rest PSS segments	**0.85 (0.71-1.0)**	0.06		
Peak PSS segments	0.99 (0.88-1.1)	0.89		
ΔPSS segments	1.1 (0.96-1.2)	0.24		
Rest PSI (%)	0.98 (0.92-1.0)	0.54		
Peak PSI (%)	**1.1 (1.0-1.1)**	**0.04**	1.1 (0.98-1.1)	0.15
ΔPSI (%)	**1.0 (1.0-1.1)**	0.08		

***** Because of multicollinearity, separate multivariate analyses for each parameter achieving a significance of p<0.05 on univariate analysis were performed, adjusted for the clinical characteristics achieving univariate significance (age, left anterior descending as infarct-related artery and multivessel disease). ** For this multivariate model, multivessel disease (OR 4.3, 95% CI 1.6-12, p=0.005) was also an independent associate of the presence of significant CAD at follow-up. *** For this multivariate model, age (OR 1.0, 95% CI 1.0-1.1, p=0.03) and multivessel disease (OR 4.0, 95% CI 1.4-11, p=0.009) were also independent associates of the presence of significant CAD at follow-up.

CI, confidence interval; PLSS, peak longitudinal systolic strain; PSI, post-systolic shortening index; PSS; post-systolic shortening; OR, odds ratio; WMSI, wall motion score index.

The addition of global ΔPLSS using this cut-off over the combined model of clinical parameters (age, LAD as IRA, multivessel disease) and conventional visual analysis (≥2 stress-induced wall motion abnormalities) had incremental value for the prediction of significant CAD at follow-up post-myocardial infarction (final global X^2 29.0 vs. 25.1 for combined model, p<0.05).

Conventional Vs. Quantitative DSE Analysis: Segmental Assessment

Regarding conventional visual analysis, incorporating all segments as per current clinical protocol, both ΔWMS (OR 1.002, 95% CI 1.000-1.004, p=0.04) and biphasic response (OR 1.009, 95% CI 1.003-1.015, p=0.003) were significantly associated with significant CAD in the coronary territory supplied by the respective representative segment. However, after adjustment for clinical variables (age, LAD as IRA and multivessel disease), neither parameter (ΔWMS: OR 1.00, 95% CI

Table 3. Receiver-operating characteristics curve analyses and feasibility of segmental peak longitudinal systolic strain from rest to peak stress (ΔPLSS) for the detection of a >70% stenosis in the corresponding coronary territory

Segments	Segmental ΔPLSS	Feasibility PLSS*	
	AUC (95% CI)	Rest	Peak
Left anterior descending			
Mid anteroseptal	0.58 (0.43-0.73)	90	80
Basal anteroseptal	0.50 (0.35-0.64)	98	87
Apical septum	0.50 (0.37-0.63)	100	105
Apical anterior	0.51 (0.37-0.65)	93	98
Mid anterior	0.56 (0.41-0.72)	86	85
Basal anterior	0.41 (0.29-0.54)	98	98
Apex	**0.82 (0.73-0.91)**	**96**	**101**
Left circumflex artery			
Basal posterior	0.42 (0.24-0.60)	97	96
Mid posterior	**0.74 (0.59-0.90)**	**95**	**92**
Apical lateral	0.52 (0.32-0.73)	103	102
Mid lateral	0.59 (0.39-0.78)	95	96
Basal lateral	0.48 (0.27-0.69)	100	102
Right coronary artery			
Basal inferoseptum	0.46 (0.29-0.62)	102	103
Mid inferoseptum	0.54 (0.35-0.72)	102	95
Basal inferior	0.49 (0.33-0.64)	99	105
Mid inferior	**0.71 (0.56-0.85)**	**95**	**98**
Apical inferior	0.47 (0.32-0.62)	103	103

* Reported as frequency of each segment available for analysis in the total patient population (n=105). AUC, area under the curve; CI, confidence interval.

1.00-1.00, p=0.20; biphasic response: OR 1.00, 95% CI 1.00-1.00, p=0.29) were independent associates of significant CAD.

For 2D STE analysis, using the sentinel segment technique, the optimal segment for the LAD was the apex (AUC 0.82, 0.73-0.91, p<0.001). In the LCx territory, the mid posterior (0.74, 0.59-0.90, p=0.02) and in the RCA territory, the mid inferior (AUC 0.71, 0.56-0.85, p=0.02) segments were chosen as the representative segments (Table 3). Sensitivities, specificities and diagnostic accuracies of each sentinel segment for identification of significant CAD in each specific coronary territory using the same ΔPLSS cut-off applied for global analysis (≥1.9%) were 63%, 69% and 67% respectively for the LAD, 78%, 47% and 50% respectively for the LCx and 92%, 33% and 42% respectively for the RCA territory. On generalized estimating equation analysis, larger positive value of segmental ΔPLSS was significantly associated with the presence of >70% stenosis in the coronary territory supplied by the respective representative segment (OR 1.1, 95% CI 1.1-1.2, p<0.001). Furthermore, segmental ΔPLSS remained significantly associated with the presence of significant CAD (OR 1.1, 95% CI 1.1-1.2, p<0.001) following adjustment for clinical parameters (age, LAD as IRA and multivessel disease).

Odds ratios for the risk of significant CAD at follow-up with larger segmental ΔPLSS across different relevant clinical and infarct-related subgroups are shown in Figure 3.

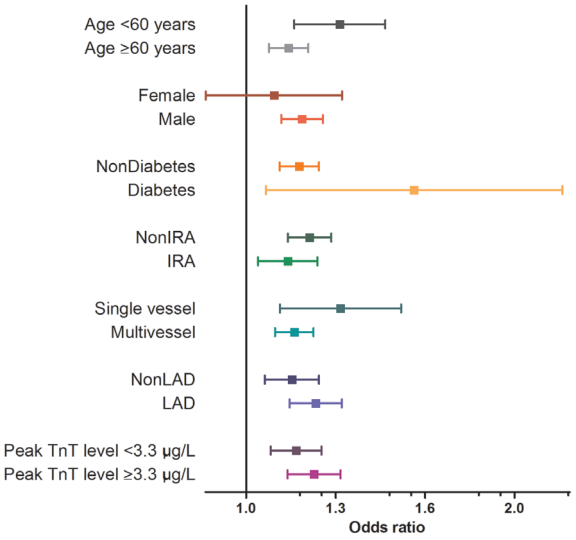

Figure 3. Odds ratios for the risk of >70% stenosis in the corresponding coronary territory at follow-up for larger (more positive increase) segmental ΔPLSS across relevant clinical and infarct subgroups. LAD, left anterior descending; IRA, infarct-related artery; PLSS, peak longitudinal systolic strain; TnT, troponin T.

In particular, segmental ΔPLSS remained significantly associated with significant CAD across age, anterior and non-anterior territory and infarct size (stratified by median value of peak troponin T level of 3.3 μg/L) subgroups. Importantly, the significant association also remained across baseline single vessel (p=0.002) or multivessel (p<0.001) disease subgroups and among IRA (p=0.006) or nonIRA (p<0.001) segment subgroups.

Reproducibility

Intra- and inter-observer variability analyses for both global and segmental PLSS are illustrated in Table 4.

Table 4. Intra- and inter-observer variability for peak longitudinal systolic strain at global (n=340 segments) and segmental (n=60 sentinel segments) level for rest and peak stage of dobutamine stress echocardiography

	Intra-observer variability		Inter-observer variability	
	ICC	**Absolute difference (%) ***	**ICC**	**Absolute difference (%) ***
Global level				
Rest	0.97	7.6	0.90	9.2
Peak	0.91	13.9	0.90	16.7
Sentinel segment				
Apex				
Rest	0.99	3.2	0.97	13.8
Peak	0.97	7.9	0.83	18.8
Mid posterior				
Rest	0.99	4.5	0.96	10.0
Peak	0.95	12.6	0.95	11.3
Mid inferior				
Rest	0.99	4.7	0.98	7.4
Peak	0.95	10.0	0.87	17.9

ICC, interclass correlation coefficient.
* Calculated as the absolute difference divided by the mean of the pair-repeated observations.

DISCUSSION

Analysis of 2DSTE longitudinal strain parameters during full-protocol DSE alongside conventional visual analysis was feasible in the majority of patients after STEMI at peak-dose as well as at rest stage. At global level, ΔPLSS was independently associated with the presence of significant CAD at follow-up, unlike ΔWMS, and provided incremental value to conventional visual analysis for detection of significant CAD at follow-up. Segmental ΔPLSS similarly demonstrated independent association with significant CAD in the corresponding coronary territory; this association persisted across key clinically relevant subgroups.

Conventional vs. quantitative DSE analysis in the post-STEMI population

Multivessel CAD, whether present at the outset[26] or developing subsequently[27] is highly prevalent in the post-STEMI population. The extent of residual and/or new ischemia after myocardial infarction is well known to relate to adverse cardiac outcomes.[14,15] Additionally, studies have shown that the identification of multivessel disease and/or ischemia by DSE provides incremental prognostic value to that identified by exercise electrocardiography or angiography.[15,28,29] However, the post-infarct setting presents significant challenges to accurate conventional DSE analysis, principally due to the presence of existing wall motion abnormalities adding an increased level of complexity to interpretation. Previous meta-analyses have shown considerable variability in the sensitivity of DSE for prediction of multivessel disease, reported as between 8% to 71%.[3,25] In the present analysis, in whom over half (52%) of our population had abnormal wall motion at rest, sensitivity of conventional wall motion analysis was correspondingly poor. Furthermore, neither ΔWMSI nor ΔWMS were independently associated with significant CAD on multivariate analyses. Several other factors may contribute to the underestimation of ischemia in this real-world heterogenous post-infarction setting including beta-blocker prescription, collateral circulations and imperfect assignment of myocardial regions to coronary arteries; wall motion abnormalities manifest at a later stage in the ischemic cascade and are likely to be affected by these factors. The use of our definition of significant diameter stenosis(es) at follow up as 70% rather than 50% as frequently used in other studies[3,25] may also have impacted on the particularly low sensitivity of our results.

The limitations of this conventional semi-quantitative evaluation of ischemia by DSE have led to the need for investigation of novel quantitative techniques applied to DSE with the potential to overcome these disadvantages. A multicenter clinical study has already demonstrated that longitudinal strain analysis provided incremental diagnostic accuracy to expert visual analysis for detection of CAD during DSE.[12] Deformation analysis at baseline coupled with its subsequent response to dobutamine stimulation may therefore enable better discrimination of different ischemic substrates.[30] However, which parameter, or combination of parameters, best reflects ischemia has not been widely studied in the post-infarction population. While PLSS is reduced in ischemia, it is also decreased in severe CAD and scarred/infarcted tissue (where the degree of reduction is proportional to the extent of transmurality of the infarction). PSS is an additional phenomenon measurable by 2DSTE occurring early after the onset of ischemia with a magnitude proportional to the severity of ischemia.[24,31] Its derivative, PSI, developed to increase specificity of this highly sensitive marker of ischemia, has been identified in a study comparing multiple 2D DSE strain parameters in 44

suspected CAD patients to be the optimal parameter to identify stress-induced ischemia.[24]

Global quantitative analysis

Notably, in our contemporary post-STEMI cohort, over one-third of whom demonstrated >70% stenosis in ≥1 major epicardial vessel at follow-up, global PLSS decreased significantly from rest to peak stress in the overall population, but in patients with significant CAD, it was significantly more impaired from rest to peak stress compared to those without evidence of significant CAD at follow-up. Previous experimental and human studies have shown that in normal segments in response to dobutamine, although peak systolic strain increases initially at low-dose dobutamine, it does not increase further (in contrast to strain rate) due to the restrictions imposed by higher heart rates on increased LV filling.[24,33] In acute ischemia in response to dobutamine, PLSS decreases significantly.[24,32] In a population of 102 patients referred for clinically-indicated DSE undergoing concomitant coronary angiography, Ng et al. showed that low-dose and pre-peak-dose strain were significantly higher than rest in subjects without significant CAD, while peak-dose strain did not increase significantly, although notably, did not decline.[12] It is important to emphasize that fundamental differences between the populations in these prior studies and the present study population are likely to have significantly influenced the magnitude of response of longitudinal strain to stress.[32] Notably, only 30% of the patients in the Ng et al. study[12] had a previous history of myocardial infarction, compared to 100% of the current study population. In the seminal paper by Voigt et al.[24], segments with scintigraphic evidence of scar, wall motion abnormalities or abnormal strain-rate patterns at rest were excluded. The pathobiology of the post-infarction setting means that longitudinal mechanics may reflect not only an underlying acute ischemic substrate but multiple other substrates: chronic ischemia/flow-limiting stenosis(es); subendocardial and/or transmural scar; at-risk border zone segments or a combination of these substrates. A decrease in PLSS despite angiographically non-significant CAD at follow-up may be a reflection of the decrement in peak stress known to be associated with any degree of mural scar (proportional to the transmurality and degree of fibrosis) after infarction even in the presence of normal flow reserve.[32] Superimposed acute ischemia and/or residual critical stenosis causing chronic hypoperfusion will induce significant decrements in strain at both low-dose and peak stress.[32]

These pathophysiological concepts are expanded with the finding of significantly more impaired global PLSS from rest to peak stress in post-STEMI patients with significant CAD at follow-up. The independent association between global ΔPLSS (and peak PLSS) and later significant CAD supports the suggestion that it

is identifying ischemia reflected by later angiographically significant CAD that is independent of, or occurring in tandem with, the severe CAD itself and/or the tissue heterogeneity as a consequence of the infarction. It is also supported by the parallel finding that global PSI, a sensitive marker of ischemia,[24,31] significantly differed between groups at peak-dose, reflecting a larger increment from rest to peak stage in patients with significant CAD. This parameter likely did not show significance at a multivariate level when combined with strong clinical predictors due to the non-specific nature of its component, PSS, blunting the differential increase seen in patients with significant CAD at peak stress.

However, it must be noted that despite high sensitivity (87%) of this cut-off of ΔPLSS for detection of angiographically important CAD, specificity and diagnostic accuracy were modest at best. A number of factors must be borne in mind when interpreting these results. Firstly, this is the first such study that we are aware of assessing the diagnostic ability of quantitative 2DSTE parameters on full-protocol DSE for significant CAD in a population composed entirely of post-infarction patients. Secondly, as discussed above, the behaviour of longitudinal strain to pharmacological stress varies significantly depending on the underlying ischemic substrate. Therefore, diagnostic accuracies (and odds ratios) for this parameter in this population may need to be interpreted accordingly. Thirdly, angiographically significant CAD may not synonymous with ischemia in all patients and vice versa – ischemia may be present in the setting of reduced coronary flow reserve (potentially identifiable by PLSS) in the absence of a fluoroscopically significant lesion. In summary, post-STEMI patients with segments not showing an active ischemic response are likely not comparable to truly normal segments (no ischemic response and no significant CAD on coronary angiography) in patients with no prior history of a myocardial infarction. Other important sources of variation in deformation analysis including the hemodynamic status of the patient need to be considered. Reassuringly, although longitudinal strain can be modestly affected by heart rate and blood pressure[34] these factors were similar between CAD and no CAD groups throughout the DSE. Finally, technical factors associated with current generation STE technology under stress conditions[35,36] should also be considered. Accurate speckle-tracking requires adequate frame rates; higher heart rates associated with peak dobutamine stress require higher frame rates and certainly may have influenced the specificity of PLSS by underestimating the maximal degree of shortening. Notably, this potential for lesser degree of shortening at peak stress was equally possible in both patient groups (those with significant CAD at follow-up and those without). Ultimately, additional standardization and/or technology updates are required prior to routine clinical use of this technique in this complex population.

Segmental quantitative analysis

In addition to global quantitative assessment, regional analysis to assess the ability of 2DSTE strain to localize ischemic territories (residual or new) was also performed. Assessment of deformation indices from each LV segment in order to detect regional impairment in myocardial performance suggestive of ischemia is cumbersome and thus to increase applicability for routine clinical use a "sentinel" segment method, representative of each coronary territory, was undertaken.[10] Firstly it is important to acknowledge that the AUCs for segmental ΔPLSS to distinguish the presence or absence of a >70% stenosis in the corresponding coronary territory are less than optimal for non-sentinel segments. Unfortunately, robust reproducibility for segmental strain even in the normal population has proved elusive with current STE techniques, and there remains a lack of a clear cut-off value of strain for each individual segment, which may vary significantly even among normal subjects.[34] More specifically, reproducibility of regional 2DSTE strain at peak-dose of DSE was recently shown to be reduced compared to global strain in a general population of 50 patients undergoing DSE.[35] This reduced reliability of segmental strain values most likely reflects the increased signal-to-noise ratio resulting from excessive myocardial motion at higher heart rates, Comparing our results to the initial study to suggest a similar sentinel segment approach,[10] a "clear-cut" superior segment was not as apparent in the LAD territory as in our study, but in both studies the apex was used as the sentinel segment for this region. For both the LCx and RCA territories in the older study, more similar variation in values across segments for each territory was seen, and representative segments were also identical for RCA territory (mid inferior) and adjacent within the posterior region (basal versus mid posterior, respectively) for the LCx territory. Notably, average AUCs were higher throughout despite the similar variation; however, in the former study, 2D strain rate was the DSE strain parameter used which likely played a major role in the differences. Additionally, due to the inherent nature of our population, certain segments may have low AUCs due to the presence of transmural infarction/scar in these regions associated with absent deformation at rest and inability to mount any response to dobutamine, therefore inability to detect significant CAD by change in deformation from rest to peak.[32]

Regarding our sentinel segment PLSS analysis, applying the same cut-off to each sentinel segment as derived from global analysis produced sensitivities no lower than 63% for each individual segment (combined sensitivity of 74%). However, diagnostic accuracies and specificities were limited, especially in non-LAD territories, a finding which correlates with the study by Hanekom et al.[10] Factors such as the dependence of the method on gray-scale image quality, as well as the potential for excessive annular motion at the base during peak stress to lead to

tracking problems in this region, are very likely to be exerting influence in these less than optimal values.[36] Importantly, segmental ΔPLSS (in contrast to ΔWMS) was significantly associated with the presence of >70% stenosis in the coronary territory supplied by those segments adjusted for significant clinical parameters. This independent association between segmental deformation and significant CAD in the corresponding territory at follow-up, in addition to the global findings, supports the hypothesis of longitudinal deformation analysis on DSE facilitating the identification of ischemic substrates in post-STEMI patients. Additionally, on subgroup analysis, segmental ΔPLSS remained independently associated with significant CAD in its corresponding territory across both anterior and non-anterior location subgroups, nonIRA as well as IRA segments and single vessel versus multivessel disease at outset subgroups, further evidence to support that this 2DSTE DSE parameter is potentially identifying hemodynamically significant stenosis(es) confirmed at follow-up angiography.

Limitations

The reliance of current speckle-tracking technology on adequate gray-scale image quality[36] means that 15% of otherwise eligible patients were excluded from the study. However, this is in line with recently published data focusing on the reproducibility of this technique in a general DSE population[35] and should also be considered in light of the 8% of unenhanced DSE studies which are uninterpretable for even conventional visual analysis.[37] The presence of significant epicardial disease on coronary angiography was used in the current study as a surrogate of ischemia; discrepancies between anatomical severity of a lesion as viewed with fluoroscopy and its functional effects on myocardial blood supply are well documented.[38] However, previous data has indicated that in patients with prior myocardial infarction, stenoses >70% are associated with a significantly reduced coronary flow reserve (≤1.5 with ≤2.0 considered abnormal).[39] Furthermore, significant multivessel disease with or without ischemia is itself an adverse prognostic factor after STEMI[15] and thus the adoption of a reproducible, novel quantitative DSE application for its identification may have significant clinical potential. The median time interval between DSE and subsequent coronary angiography is at the upper limit for time-relevant comparison (6 months). However, in addition to global findings, segmental deformation on DSE and significant CAD in the corresponding territory on angiography were independently associated despite this time interval. It is unknown whether the angiographically significant disease was present at the time of DSE or became more progressive, however, the ability of 2DSTE parameters to identify ischemia at an earlier stage of the ischemic cascade than visual analysis has been demonstrated.[40] Specificity of 2DSTE strain on DSE may be further re-

duced in patient populations not biased towards clinically or functionally directed coronary angiography. Quantitative analysis at the low-dose stage of dobutamine was not explored in detail. Although low-dose was considered in the conventional analysis arm so that the presence of the biphasic response by wall motion analysis could be demonstrated, it was not added at 2DSTE level to avoid further increasing complexity regarding interpretation in this already complex population. The cut-off derived for global ΔPLSS to predict significant CAD was also applied to our segmental PLSS analysis, in order to investigate, in the absence of robust reproducibility data for segmental strain, how this cut-off derived from the most reproducible deformation parameter would perform in the sentinel segments. Moreover, the suggested cut-off derived on ROC curve analysis was not tested in a validation group. The results of our study including this derived cut-off need to be confirmed in larger-scale prospective analyses ideally across multiple vendor platforms and using clinically relevant outcomes (e.g. cardiovascular death, repeat myocardial infarction) and incorporating specific ischemia testing (eg fractional flow reserve).

Conclusions

2DSTE strain analysis is feasible on full-protocol DSE after STEMI and represents a promising new quantitative technique to detect significant angiographic CAD at follow-up.

PLSS investigated at rest and peak stage of DSE was the optimal parameter to detect the ischemic substrate in stable patients after myocardial infarction and provided incremental value to conventional visual wall analysis. However, low specificity, segment-to-segment heterogeneity and challenges inherent to current generation technology limit routine clinical adoption of this method at the present time.

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