Quantification of low-dose dobutamine stress using speckle tracking echocardiography in coronary artery disease

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Aims We sought to evaluate the utility of speckle tracking echocardiography (STE) for detecting left ventricular (LV) mechanical abnormalities during low-dose (20 μg) dobutamine stress (DSE).

Methods and results Twenty-nine patients (56 ± 12 years) with a history of recent acute coronary events (ACE) underwent STE-DSE. Left ventricular images, sampled at frame rates 70–100 Hz, were analysed off-line (Echopac BT 6.0.0). Velocity, strain, and rotational imaging were performed. Twenty patients had LV ejection fraction (EF) >40% (Group 1) whereas nine patients had LV EF <40% (Group 2). Average heart and frame rates were identical during DSE in the two groups (P = ns). Global circumferential strain (%) was significantly lower in Group 2 compared with Group 1 (10.65 ± 5.30 vs. 16.82 ± 6.61; P < 0.05) at rest and during peak stress (14.72 ± 6.51 vs. 21.13 ± 7.2; P < 0.05). The global peak rotation rate (degree/s) was however, higher at rest in Group 2 (70 ± 97 vs. 19 ± 67; P < 0.05) and 20 μg stress. Peak systolic velocity increased in three of the four LV walls at 20 μg (in Groups 1 and 2). A global rotational rate increased significantly at 20 μg during systole in both the groups, but was unchanged in Group 2 during diastole.

Conclusions Speckle tracking echocardiography dobutamine stress appears to provide comprehensive information on LV mechanical status in the aftermath of ACE. The modality may help risk stratify such patients.

KEYWORDS
Speckle tracking echocardiography; 2D strain; Coronary artery disease; Left ventricular function; Dobutamine stress echocardiography

Introduction

Accurate assessment of left ventricular (LV) function in coronary artery disease (CAD) is essential for risk assessment and patient management. However, assessment of LV function in the background of CAD by subjective analysis, conventional echocardiography, and regional quantification by tissue velocity echocardiography (TVE) continue to have their limitations.1 Though TVE has been a major advancement over the past decade with numerous studies validating quantification of longitudinal motion of the heart,2 the angle-dependent TVE is incapable to quantify radial, circumferential, and rotational mechanics of the LV. Initial experience by our group using the non-Doppler-based speckle tracking echocardiography (STE, alias 2D strain) has shown its capability to register rotational (torsion) abnormalities with favourable signal-to-noise ratio during balloon inflation in the catheterization laboratory.3 Moreover, longitudinal systolic strain rate and strain by STE enable detection of significantly diseased coronary arteries at rest.4 Most recently, longitudinal strain immediately after primary reperfusion therapy has been shown to be an excellent predictor of LV remodelling and adverse events.5 However, application of STE during stress echocardiography in human subjects has hitherto been non-existent.

Methods

Study population

Twenty-nine patients (22 males), mean age of 56 ± 12 years, with known CAD and associated co-morbidities such as type 2 diabetes (DM) and systemic arterial hypertension (HTN) and predominantly...
medicated with angiotensin receptor blockers and beta-blockers were studied. Coronary artery disease was defined by ST elevation or non-ST elevation myocardial infarction documented by ECG, elevated cardiac enzymes, and/or the presence of wall motion abnormality by echocardiography. Twenty patients with LV ejection fraction (EF) $>40\%$ (Group 1) and nine patients with LVEF $<40\%$ (Group 2) with both groups being in sinus rhythm and considered for coronary angiogram and revascularization were included. They underwent low-dose STE-quantified dobutamine stress echocardiography (STE-DSE). Patients with haemodynamic and electrical instability, structural heart disease were excluded.

The institutional review board of the Vivus-BMJ Heart Centre at Bangalore, India, approved the study protocol. All study subjects gave informed consent.

Conventional echocardiography
Echocardiography was performed on a commercial Vivid 7 dimension equipment (General Electric, Vingmed, Horten, Norway) using an adult matrix probe. The images were acquired from parasternal long- and short axis as well as in apical four-, three-, and two-chamber windows. Left ventricular ejection fraction was calculated using the modified Simpson’s method.

Speckle tracking echocardiography
Left ventricular images sampled at appropriate frame rates during DSE were post-processed using the STE software (Echopac 6.0.0) as previously described. Briefly, the displacement of speckles of LV myocardium (the acoustic markers) in each spot was tracked from frame to frame in each of the apical and short-axis views. The software package then automatically tracked the motion through the rest of the cardiac cycle, providing the LV strain (%) profile by default. Rotational and velocity imaging were performed step by step just by highlighting the key to the respective parameters inbuilt in the software. The same procedure was applied at rest, during DSE at 20 $\mu$g, as well as during recovery stage. Left ventricular longitudinal data were collected from the bases of the septum, lateral, inferior, and anterior walls.

Longitudinal parameters
Global peak systolic strain rate and end-systolic strain % along with regional peak systolic velocities (PSV) and early diastolic velocities ($E’$ and $A’$) were obtained from the apical images. In addition to that, strain rate at diastole was also estimated during both the early (SRE) and the late phases of diastole (SRA).

Circumferential parameters
Global circumferential strain rate at systole (SRS) and diastole (SRE and SRA) were also registered, taking the average of six short-axis LV segments. Global peak rotation rate and total rotation were obtained by tracking the parasternal short-axis images at the papillary muscle level during the above-mentioned three phases of DSE (Figure 1).

Dobutamine stress echocardiography
After conventional transthoracic echocardiography, a low-dose (20 $\mu$g) STE enhanced-DSE was performed. All acquired LV images were digitally stored and post-processed on Echopac BT 6.0.0 workstation (GE Vivid 7). Frame rates were manually adjusted according to the heart rates during different stages of DSE.

Statistical methods
A PC-based version of Statistica version 6.0 (Statsoft, USA) was used for data analysis. A $P$-value of $<0.05$ was considered
statistically significant. Data (mean ± SD) were compared using unpaired t-test and ANOVA.

**Intra-observer variability**

Intra-observer variability was calculated by Pearson’s correlation coefficient and by calculating mean differences and the standard deviation of those differences. Data (below) are expressed as mean ± standard deviation (95% CI) along with the respective r-values.

The values for global circumferential strain (%) were 0.21 ± 2.7 (–1.9, 9.4; r = 0.93), for maximum positive rotation rate during peak systole (degrees/s) 0.15 ± 15 (–9.8, 10.1; r = 0.75), for maximum negative rotation rate during peak systole (degrees/s) –5.45 ± 21 (–18.5, 7.6; r = 0.82), for rotation rate (degrees/s) during late (A) phase 4.1 ± 14 (–4.7, 12.9; r = 0.66), and for peak systolic global rotation (degree), the value was –0.66 ± 1.7 (–1.7, 0.4; r = 0.63). Figure 2 shows the intra-observer variability regarding the diastolic component of the rotation rate.

Mean difference for global longitudinal strain rate (1/s) during systole was 0.07 ± 0.08 (0.01, 0.11; r = 0.84), global longitudinal strain rate (1/s) during early diastole was 0.08 ± 0.1 (0.02, 0.15; r = 0.92), and global longitudinal strain rate (1/s) at late diastole was 0.02 ± 0.12 (–0.05, 0.09; r = 0.92).

**Results**

The mean age was 56 ± 9 years in Group 2, and 54 ± 8 years in Group 1; P > 0.05. At rest, mean systolic blood pressure (mmHg) was 135 ± 17 vs. 127 ± 15; P > 0.05, and mean diastolic blood pressure was 81 ± 8 vs. 76 ± 9; P > 0.05 in the respective two groups. Plasma glucose and creatinine levels did not differ (Table 1).

**Between-group comparisons (unpaired t-test)**

At rest, the heart rate (bpm) was 84 ± 15 in Group 2, 75 ± 16 in Group 1; P > 0.05. The corresponding frame rate (Hz) was 59 ± 8 vs. 53 ± 9; P > 0.05. At 20 μg, the heart rate was...

Table 1 Clinical, biochemical, and angiographic data of the study subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>LVEF &gt;40%</th>
<th>LVEF &lt;40%</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Male/female</td>
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<td>7/2</td>
<td></td>
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<tr>
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<td>53.0 ± 10.7</td>
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<td>5</td>
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<td></td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HTN + DM</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ARB/ACEI</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>15</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>138.3 ± 17.9</td>
<td>128.7 ± 14.5</td>
<td>0.10</td>
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<tr>
<td>DBP (mmHg)</td>
<td>81.1 ± 9.0</td>
<td>82.5 ± 8.8</td>
<td>0.70</td>
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<td>Haemoglobin (g/dL)</td>
<td>12.9 ± 1.6</td>
<td>13.2 ± 1.1</td>
<td>0.60</td>
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<tr>
<td>Fasting plasma glucose (mg/L)</td>
<td>145.3 ± 63.4</td>
<td>148.5 ± 79.5</td>
<td>0.90</td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.2</td>
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<td>SYD</td>
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<td>5</td>
<td></td>
</tr>
<tr>
<td>DVD</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MVD</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

HTN, systemic hypertension; DM, type 2 diabetes; ARB/ACEI, angiotensin receptor blockers/angiotensin-converting enzyme inhibitors; SBP, systolic blood pressure; DBP, diastolic blood pressure; SYD, single-vessel disease; DVD, double-vessel disease; MVD, multivessel disease.
Speckle quantification of apical four- and two-chamber views: LV regional analysis
At rest, the SRE (1/s) in the lateral wall was significantly lower in Group 2 compared with Group 1 (0.59 ± 0.4 vs. 0.98 ± 0.5; P < 0.05). There was no significant difference between the two groups at 20 µg and during recovery. In the anterior wall, the SRE (1/s) was significantly lower in Group 2 (0.6 ± 0.35 vs. 1.2 ± 0.64; P < 0.01), the displacement (mm) was similarly lower in the same group (4.5 ± 2.4 vs. 9.0 ± 2.7; P < 0.01) at rest. At 20 µg, systolic strain rate (1/s) was marginally lower in Group 2 (0.9 ± 0.4 vs. 1.6 ± 0.65; P = 0.05) in the anterior wall. In the recovery period, there was no significant difference between the variables of the two groups.

Speckle quantification of parasternal short-axis images: the global data
At rest, the circumferential strain (%) was significantly lower in Group 2 compared with Group 1 (10.65 ± 5.30 vs. 16.82 ± 6.61; P < 0.05).

At 20 µg DSE, the global % continued to be lower in the same group (14.72 ± 6.51 vs. 21.13 ± 7.2; P < 0.05). Similarly, the global peak rotation rate (degree/s) was higher in Group 2 (70 ± 97 vs. 19 ± 67; P < 0.05).

At recovery, the global SRE (1/s) was significantly lower in Group 1 (0.97 ± 0.3 vs. 1.44 ± 0.6; P < 0.05). The global % was significantly lower in Group 2 (13.5 ± 3.9 vs. 21.2 ± 7.2; P < 0.01). Global peak rotation rate (degree/s) was significantly higher in Group 2 compared with Group 1 (43.12 ± 14.75 vs. 7.85 ± 47.72; P < 0.05), also in the recovery phase.

Within-group comparison using ANOVA followed by Scheffe’s test
Patients with LVEF <40% (LV longitudinal data from apical images)
In the septum, peak systolic velocity (PSV) and A’ velocities (cm/s) were significantly higher at 20 µg compared with rest. (For PSV: 4.7 ± 1.8 vs. 8.0 ± 2.5; P < 0.01 and for A’: 5.9 ± 1.6 vs. 8.8 ± 2.7; P < 0.05.) In the lateral wall, PSV (cm/s) and SRS (1/s) were significantly higher at 20 µg compared with rest. (For PSV: 4.1 ± 1.5 vs. 6.7 ± 2.3; P < 0.05 and for SRS: 0.6 ± 0.2 vs. 1.2 ± 0.5; P < 0.05.) In the inferior wall, PSV (cm/s) was significantly higher at 20 µg compared with rest (5.4 ± 0.98 vs. 7.95 ± 2.46; P < 0.05). In the anterior wall, A’ velocity (cm/s) was significantly higher at 20 µg compared with rest (4.5 ± 1.6 vs. 7.95 ± 2.65; P < 0.01) and A’ velocity was also significantly higher at recovery compared with rest (4.5 ± 1.6 vs. 6.99 ± 2.32; P < 0.05).

Analysis of short-axis images (global circumferential data)
From parasternal short-axis view, the GSSR (1/s), the SRA (1/s), and the global peak rotation rate (degree/s) were significantly higher at 20 µg compared with rest. (For GSSR: 0.7 ± 0.5 vs. 1.42 ± 0.48; P < 0.05, for SRA: 0.3 ± 0.18 vs. 1.0 ± 0.46; P < 0.05, and for global peak rotation rate: 37.4 ± 17.5 vs. 67.0 ± 36.0; P < 0.05.)

Patients with LVEF >40% (LV longitudinal data from apical images)
In the septum, the PSV, the A’ velocities (cm/s), and the SRA (1/s) were significantly higher at 20 µg compared with rest. (For PSV: 5.4 ± 1.5 vs. 8.0 ± 1.6; P < 0.01, for A’: 5.9 ± 1.3 vs. 8.1 ± 2.3; P < 0.05, and for SRA: 0.7 ± 0.2 vs. 1.4 ± 0.8; P < 0.05.)

In the lateral wall, the SRS (1/s) was significantly higher at 20 µg compared with rest (0.9 ± 0.4 vs. 1.4 ± 0.7; P < 0.05). In the inferior wall, the A’ velocity (cm/s) was significantly higher at recovery compared with rest (6.7 ± 1.9 vs. 9.4 ± 1.8; P < 0.05). In the anterior wall, the A’ velocity (cm/s) was significantly higher at 20 µg compared with rest (5.4 ± 1.7 vs. 7.5 ± 1.9; P < 0.05), the SRS (1/s) was significantly higher at 20 µg compared with rest (0.93 ± 0.6 vs. 1.56 ± 0.6; P < 0.05), and the variable was also significantly higher at recovery compared with 20 µg (1.56 ± 0.65 vs. 0.9 ± 0.3; P < 0.05).

Analysis of short-axis images
The circumferential SRS (1/s) and SR E/A ratio were significantly higher at 20 µg compared with rest. (For SRS: 0.9 ± 0.5 vs. 1.8 ± 0.8; 0.05 and for SR E/A: 2.93 ± 1.93 vs. 1.50 ± 0.41; P < 0.05.)

Discussion
From the results of our study using STE in CAD, it can be shown that patients in the group with reduced LV function secondary to an ischaemic insult have decreased global circumferential strain (%) both at rest and during low-dose DSE. These patients also have decreased circumferential and longitudinal strain rate (1/s) whereas global rotation rate increased with DSE, probably as a compensatory response. On the contrary, systolic and diastolic strain rate improved at stress in the other group of patients with LVEF >40%. These findings are comparable with the data that emerged from our lab recently. With the vexed issue about difficulty in tracking speckle at increasing heart rate, this study focuses on this important aspect and looks at LV motion at moderately higher heart rates obtained with low-dose DSE, in order to maintain the superior signal-to-noise ratio at frame rates appropriate for the currently available Echopac software.

Utility of STE is being increasingly demonstrated in various clinical scenarios. It is well known that quantification of diastolic function at higher heart rates may not be feasible because conventional Doppler invariably results in fused mitral pulse wave velocities in tachycardia. Since in the current study, we have shown blunted rotational diastolic response to 20 µg of dobutamine in patients with reduced LVEF, STE-DSE could be used to better discern diastolic abnormalities in patients with LV systolic dysfunction. Given the good reproducibility of the data, it can be argued that evaluation of LV diastolic function could be more comprehensive and accurate by STE using multiple variables, given the limitation of E/E’ ratio using pulsed-wave Doppler-based tissue velocity imaging. A recent study by Gorcsan et al. has shown that a combination of longitudinal and radial dyssynchrony is superior to either method alone in predicting favourable outcome after cardiac resynchronization therapy. The investigators used STE to identify radial dyssynchrony and because of...
the high signal-to-noise ratio, it was rather easy to quantify radial dysynchrony in a clinically conceivable manner. Though the study was performed at rest, it is possible that a better outcome could be expected if dysynchrony could be unmasked at low-dose DSE, since more needs to be done in the field of dysynchrony imaging.

Stress echocardiography is the cornerstone of diagnosis of CAD by unveiling the supply-demand mismatch of the LV during stress, classically at peak stress except in cases of viability assessment. Importance of analysis of intermediate stages of stress data, however, is lacking substantially. Recent data have shown that intermediate stages are even more useful in certain cases where assessment of LV volume could guide the occurrence of CAD. The study has shown that the acquisition and interpretation of intermediate stages of exercise in addition to peak exercise improves the detection of CAD and allows a better physiologic evaluation of the severity of coronary stenosis. Our study using the low-dose DSE supports the concept.

Left ventricular diastolic dysfunction/failure and the need for advanced imaging technique at rest and during peak stress

The CHARMES (the CHARM Echocardiographic Substudy) study demonstrated the prognostic significance and need for objective evidence of LV diastolic dysfunction in patients with heart failure with preserved systolic function (LVEF > 40%). Unlike in the CHARMES study, in our study the conventional E/A ratio was elevated in patients with LVEF < 40%, though left atrial inner dimension was similar in both the groups, making it difficult to use conventional Doppler data to classify patients with diastolic dysfunction/failure because of the load dependence of the LV diastolic variables. Low-intensity physical stress, however, could identify patients with mild to moderate heart failure with low LVEF that also have higher E/E' ratio that has a

### Table 2  Conventional echocardiographic data

<table>
<thead>
<tr>
<th>Variables</th>
<th>LVEF &gt;40%</th>
<th>LVEF &lt;40%</th>
<th>P-value</th>
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<tr>
<td>IVSd (mm)</td>
<td>10.16 ± 5.93</td>
<td>9.63 ± 2.44</td>
<td>0.80</td>
</tr>
<tr>
<td>LVPWd (mm)</td>
<td>7.30 ± 3.87</td>
<td>9.63 ± 3.33</td>
<td>0.20</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>25.71 ± 5.40</td>
<td>29.63 ± 3.54</td>
<td>0.10</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>45.43 ± 11.49</td>
<td>50.88 ± 5.56</td>
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</tr>
<tr>
<td>LVEF (%)</td>
<td>47.28 ± 3.81</td>
<td>29.88 ± 7.37</td>
<td>0.001</td>
</tr>
<tr>
<td>Ao-wave (cm/s)</td>
<td>1.11 ± 0.32</td>
<td>1.08 ± 0.28</td>
<td>0.80</td>
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<tr>
<td>E-wave (cm/s)</td>
<td>0.63 ± 1.16</td>
<td>0.705 ± 0.13</td>
<td>0.30</td>
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<tr>
<td>A-wave (cm/s)</td>
<td>0.85 ± 1.99</td>
<td>0.60 ± 0.16</td>
<td>0.01</td>
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<tr>
<td>E/A ratio</td>
<td>0.77 ± 0.24</td>
<td>1.26 ± 0.47</td>
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IVSd, interventricular septal thickness in diastole; LVPWd, left ventricular posterior wall thickness in diastole; LA, left atrial size; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; Ao-wave, aortic peak ejection velocity; E-wave, E-wave velocity of the mitral valve inflow; A-wave, A-wave velocity of the mitral valve inflow.

*P < 0.05 is statistically significant.

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**Figure 3** Bar diagram showing rotational data during rest and 20 µg dobutamine stress in the two groups. *P < 0.01, **P < 0.01, ***P < 0.001. NS, non-significant. Error bar = ±SD.

**Figure 4** Decreased longitudinal strain (%) at rest in a patient with coronary artery disease (predominant left anterior descending artery lesion).
direct bearing on peak oxygen consumption. Although the former study could have a population with so-called HFNEF, the latter study had population with heart failure that also had a low LVEF (10–45%). A European consensus guideline therefore suggests extensive investigation to diagnose HFNEF. However, the subject is still controversial and clinically challenging and it is intriguing to speculate that STE with or without stress could, to some extent, help establish a more (patho) physiologic basis of HFNEF by using multiple parameters such as strain and rotational data both in systole and in diastole, particularly during stress (Figure 3).

Rotational and deformation imaging using STE-DSE
The physiological sequence of LV rotation and deformation in myocardial mechanics has been clearly demonstrated. In this study, we have shown that speckle quantification of LV rotational motions is feasible during low-dose DSE. Total rotation rate in diastole may identify patients with more severe ischaemic myocardial dysfunction, as we have shown in this study (Figure 3). Also, global strain has been shown to be an excellent predictor of myocardial infarct size in CAD (Figure 4). Speckle tracking echocardiography has also been shown to be suitable for non-invasive quantification of LV regional function in CAD. Not only that the degrees of systolic twist (sum of differences between apical and basal rotation) and diastolic unwinding has shown to be decreased in LV systolic dysfunction in anterior wall myocardial infarction.

Study limitations
The patient selection was confined to those undergoing coronary angiography following a coronary event, thus the inference from this study would be limited to these patients only. Furthermore, the lack of controls in our study precludes us to provide any normal data for the strain and rotational imaging during STE-DSE.

Acknowledgement
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Conflict of interest: none declared.

Funding
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References