Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality

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Aims Non-invasive echocardiographic detection of coronary artery disease (CAD), even in left main or three-vessel CAD, usually requires a stress test since regional wall motion abnormalities (RWMA) are not always evident at rest. Strain is a more sensitive parameter of myocardial systolic function and may be abnormal in patients with severe CAD.

Methods and results We evaluated whether peak systolic longitudinal strain (PSLS) of left ventricle using 2D speckle tracking method might be useful for screening of severe CAD. One hundred and eight patients who underwent echocardiography and coronary angiography were evaluated. Patients were grouped according to the coronary angiographic findings as follows; high-risk group with left main or three-vessel CAD ($n = 38$), low-risk group with one- or two-vessel CAD ($n = 28$), and control group without CAD ($n = 30$).

PSLSs of all left ventricular segments were obtained successfully in 96 (89%) patients. None had RWMA at resting echocardiogram. PSLS was significantly reduced, especially in mid- and basal segments, in the high-risk group. Receiver operating characteristic (ROC) curve analysis demonstrated that mid- and basal PSLSs could effectively detect patients with severe CAD (area under ROC curve $= 0.83$, 95% CI 0.75–0.91). According to ROC curve analysis, $-17.9\%$ appears to be a helpful cutoff value for discriminating those with severe CAD (specificity 79% and sensitivity 79%).

Conclusion PSLS at rest was significantly lower in patients with left main or three-vessel CAD without RWMA, and might be useful for identifying patients with a severe CAD.

KEYWORDS Ventricular function; Myocardial ischaemia; Coronary stenosis

Introduction

Patients with left main (LM) coronary artery disease (CAD) or three-vessel CAD are a well-known high-risk subset. However, resting left ventricular (LV) wall motions are usually normal at rest in these patients, unless there is a history of previous myocardial infarction or myocardial stunning.

It has been previously reported that tissue Doppler longitudinal velocity is reduced in patients with three-vessel CAD, but the number of study patients was small and results were inconsistent. With technical improvements in the temporal and spatial resolutions of two-dimensional (2D) echocardiography, LV peak systolic longitudinal strain (PSLS) can now be measured using the 2D speckle tracking method. This method might provide a useful means of measuring LV long-axis function, and might detect subtle changes in LV systolic function which could be caused by myocardial ischaemia. Recently, a semi-automated algorithm for automated function imaging (AFI) was devised that can assist PSLs measurements. This method can provide quantitative measurements of global and segmental PSLs using a simple bull’s eye display.

In this study, we hypothesized that repetitive ischaemic insults to LV, which occurs with LM and three-vessel CAD, would reduce systolic longitudinal function, although resting regional wall motion remains normal. Therefore, we aimed to evaluate whether global and segmental PSLs measured by the 2D speckle tracking method with AFI could be useful for detecting severe CAD.
Methods

Study subjects

This research investigation was approved by the ethical committee of the institutional review board of our hospital. We evaluated 108 consecutive patients who met the following inclusion criteria; (i) evaluation of angina by both echocardiography and coronary angiography, (ii) stable vital signs with normal systolic function and wall motion at rest, (iii) normal sinus rhythm without left bundle branch block, (iv) no valvular stenosis or regurgitation of more than mild degree, and (v) consent to participate in the study. After excluding 12 patients whose echocardiographic images were unsuitable for strain measurements, 96 patients were enrolled in the present study.

Echocardiographic examination

Conventional 2D echocardiographic examinations were performed using a Vivid 7™ system (GE Vingmed; Horten, Norway) with a 3.5 MHz transducer. Examinations included measurements of cardiac dimensions, volumes, and LV ejection fraction, as described previously.7 We obtained 2D grey scale harmonic images using a 3.5 MHz transducer in the apical long-axis, four-chamber, and two-chamber views for the global and segmental analysis of PSLS. All images were obtained at a frame rate of 60–100 frames/s without dual focusing. Three consecutive cardiac cycles were saved in digital format. Strain analysis was done off-line by one investigator unaware of angiographic results using EchoPAC® (BT 06.6.1.0, GE Vingmed; Horten, Norway) with AFI as described previously.8 In the apical long-axis view, we defined the aortic valve closing time, which was also used as reference values in two-chamber and four-chamber view. In each apical view, we defined three endocardial points which were two points of basal LV at both side of mitral annulus and one at LV apex at end-systolic period. Then the software automatically provided three lines along with endocardial, mid-myocardial, and epicardial layers which follow each myocardial layer by speckle tracking algorithm. After adjusting the region of interest to include entire myocardial layer, we validated the tracking quality throughout the cardiac cycle. Then automated algorithm provided the segmental PSLS in bull’s eye display (Figure 1). Global PSLS was defined as an average value of the 16 segmental PSLSs of an LV. Additionally, basal, mid- or apical segmental PSLS was defined as an average value of PSLS of the each corresponding six segments (four segments for the apex).

Coronary angiography

Angiographic findings were assessed by an experienced interventional cardiologist who was unaware of patient’s clinical and echocardiographic results. Coronary angiograms were visually assessed for all coronary lesions in two orthogonal planes. Lesion locations were assessed and percent diameter stenosis was measured for each coronary lesion according to the American Heart Association classification. We assessed the number of affected vessels, using a cutoff of percent diameter stenosis >70% for three epicardial vessels and >50% for LM coronary artery.9,10 High grade stenotic lesions (HSL) were defined as total or subtotal obstructions with antegrade TIMI flows of grade 0, 1, or 2. Patients were grouped according to angiographic results as follows; (i) LM or three-vessel CAD—high-risk group, (ii) 1- or 2-vessel CAD—low-risk group, and (iii) no CAD—normal control group.

Statistical analysis

Statistical analysis was performed using SAS software (version 9.1, SAS Institute, Cary, NC, USA). Data are presented as means ± standard deviation or as frequencies. The Chi-square test or Fisher’s exact test was used to compare frequencies. One-way analysis of variance with post hoc analysis by Bonferroni’s correction was used to compare descriptive parameters after confirming normal distributions. Receiver operating characteristic (ROC) curve analysis was used to identify parameters that best predicted the presence of high-risk CAD. To investigate intra- and interpersonal measurement variability, measurements were performed off-line by two investigators on 48 randomly selected cases and the intra-class correlation coefficients (ICC) were calculated. ICC of global PSLS for intraobserver measurements was 0.89 (P < 0.001, 95% confidence interval (CI) 0.81–0.94) and for interobserver measurements was 0.89 (P < 0.001, 95% CI 0.77–0.94). ICC of segmental PSLS for intraobserver measurements were 0.86 (P < 0.001, 95% CI 0.77–0.92) in basal segment, 0.94 (P < 0.001, 95% CI 0.89–0.96) in mid-segment, and 0.85 (P < 0.001, 95% CI 0.74–0.91) in apical segment, respectively. ICC of segmental PSLS for interobserver measurements was 0.89 (P < 0.001, 95% CI 0.81–0.94) in basal segment, 0.91 (P < 0.001, 95% CI 0.84–0.95) in mid-segment, and 0.74 (P < 0.001, 95% CI 0.55–0.85) in apical segment, respectively.

![Figure 1](https://academic.oup.com/ehjcimaging/article-abstract/10/5/695/2396908/2)

Figure 1 Measurement of peak systolic longitudinal strain (PSLS). The left column shows a representative case from the normal group and the right column shows that of high-risk patients with left main coronary artery stenosis. The first row shows the speckle tracking process in apical three-chamber view. In second and third rows, strain curves of each segment and segmental PSLS values are displayed. In the last row, segmental PSLSs are present as a ‘bull’s eye’ display. Note that the PSLS values of high-risk patients are lower than those of normal patients especially in mid- and basal segments.
Results

Clinical characteristics

PSLS was measured successfully with good tracking quality in 96 (89%) of the 108 patients initially enrolled in this study. Clinical characteristics according to study group are shown in Table 1. Their mean age was 59 ± 9 and 68 (70.8%) were men. No significant differences were found between the high-risk group and the other two groups in terms of age, sex, blood pressures, or clinical risk factors. However, patients in the low-risk group were older than those in the normal group. Although statistically insignificant, diabetic patients were more frequently enrolled in the high-risk group than in the low-risk group (57.9 vs. 21.4%, P = 0.003). No significant differences were found between the three study groups in terms of LV ejection fraction. Interestingly, LV fractional shortening was significantly higher in the high-risk group than in the normal group (42 ± 6 vs. 38 ± 5%, P = 0.019).

Echocardiographic and angiographic data

Angiographic data and clinical diagnoses are presented in Table 2. Although statistically insignificant, patients with unstable angina with or without resting pain were more frequently enrolled in the high-risk group than in the other two groups, and HSL was more frequent in the high-risk group than in the low-risk group (57.9 vs. 21.4%, P = 0.003).

Table 1: Clinical characteristics by study group

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>High risk (n = 38)</th>
<th>Low risk (n = 28)</th>
<th>Normal (n = 30)</th>
<th>Total (n = 96)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>25 (65.8)</td>
<td>25 (89.3)</td>
<td>18 (60.0)</td>
<td>68 (70.8)</td>
<td>0.034</td>
</tr>
<tr>
<td>Age (year)</td>
<td>60 ± 10</td>
<td>62 ± 8†</td>
<td>56 ± 9</td>
<td>59 ± 9</td>
<td>0.044</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67 ± 12</td>
<td>70 ± 8</td>
<td>65 ± 7</td>
<td>67 ± 10</td>
<td>0.099</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 ± 10</td>
<td>168 ± 7</td>
<td>164 ± 7</td>
<td>165 ± 9</td>
<td>0.058</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.72 ± 0.20</td>
<td>1.80 ± 0.13</td>
<td>1.71 ± 0.12</td>
<td>1.74 ± 0.16</td>
<td>0.082</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1 ± 2.5</td>
<td>24.8 ± 1.9</td>
<td>23.9 ± 1.7</td>
<td>24.6 ± 2.1</td>
<td>0.078</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>16 (42.1)</td>
<td>8 (28.6)</td>
<td>5 (16.7)</td>
<td>29 (30.2)</td>
<td>0.074</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>25 (65.8)</td>
<td>20 (71.4)</td>
<td>14 (46.7)</td>
<td>59 (61.5)</td>
<td>0.120</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>16 (42.1)</td>
<td>13 (46.4)</td>
<td>5 (16.7)</td>
<td>34 (35.4)</td>
<td>0.033</td>
</tr>
<tr>
<td>Cerebrovascular accident, n (%)</td>
<td>5 (13.2)</td>
<td>2 (7.1)</td>
<td>0 (0.0)</td>
<td>7 (7.3)</td>
<td>0.110</td>
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<tr>
<td>Smoking, n (%)</td>
<td>13 (35.9)</td>
<td>7 (25.0)</td>
<td>5 (16.7)</td>
<td>27 (28.1)</td>
<td>0.105</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 ± 19</td>
<td>125 ± 19</td>
<td>127 ± 20</td>
<td>126 ± 19</td>
<td>0.949</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>72 ± 12</td>
<td>75 ± 10</td>
<td>76 ± 13</td>
<td>74 ± 12</td>
<td>0.391</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68 ± 910</td>
<td>60 ± 7</td>
<td>61 ± 8</td>
<td>64 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>146 ± 69†</td>
<td>123 ± 43</td>
<td>106 ± 37</td>
<td>127 ± 56</td>
<td>0.012</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>167 ± 36</td>
<td>167 ± 43</td>
<td>171 ± 33</td>
<td>168 ± 37</td>
<td>0.920</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.91 ± 0.22</td>
<td>1.04 ± 0.32†</td>
<td>0.88 ± 0.16</td>
<td>0.94 ± 0.25</td>
<td>0.030</td>
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<tr>
<td>Haemoglobin (g/dL)</td>
<td>13.6 ± 1.9</td>
<td>13.9 ± 1.2</td>
<td>14.0 ± 1.4</td>
<td>13.8 ± 1.6</td>
<td>0.408</td>
</tr>
<tr>
<td>Medication</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>16 (42.1%)†</td>
<td>16 (57.1%)†</td>
<td>2 (6.7%)</td>
<td>34 (35.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARB and/or ACE inhibitor</td>
<td>17 (44.7%)†</td>
<td>15 (53.6%)†</td>
<td>2 (6.7%)</td>
<td>34 (35.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>15 (39.5%)</td>
<td>13 (46.4%)</td>
<td>7 (23.3%)</td>
<td>35 (36.5%)</td>
<td>0.167</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7 (18.4%)</td>
<td>4 (13.5%)</td>
<td>2 (6.7%)</td>
<td>13 (13.5%)</td>
<td>0.341</td>
</tr>
<tr>
<td>Nitrate agent</td>
<td>7 (18.4%)</td>
<td>6 (21.4%)</td>
<td>2 (6.7%)</td>
<td>15 (15.6%)</td>
<td>0.226</td>
</tr>
</tbody>
</table>

CVA, cerebrovascular accident; ARB, angiotensin II receptor antagonist; ACE, angiotensin-converting enzyme.

*P-value using Chi-square test or one-way analysis of variance with post hoc analysis with Bonferroni’s correction. †P < 0.05 and †P < 0.001 compared with the normal group. ‡P < 0.05 compared with the low-risk group.

Global and segmental peak systolic longitudinal strains

Global and segmental PSLs in the three study groups are presented in Table 3 and Figure 2. Global and segmental PSLs were lower in the high-risk group than in the other two groups. Segmentation analysis showed that reductions in PSLs were more evident in the LV mid- and basal segments than in the apical segment.

Receiver operating characteristic analysis and the diagnosis of high-risk coronary artery disease

The results of ROC analyses for the detection of high-risk CAD are shown in Figure 3 and Table 4. Operational cutoff values with corresponding predictive characteristics are presented in Table 4. According to ROC curve analysis, the optimal cutoff value for mid- and basal PSLs for the detection of high-risk CAD was −17.9% (sensitivity = 78.9% and specificity = 79.3%).
is frequently required to improve long-term prognosis in these subsets of patients with symptoms.\textsuperscript{11,12} Although exercise or pharmacological stress testing has a higher sensitivity for three-vessel and LM CAD, the risk of stress test is higher also in this patient population.\textsuperscript{13} Furthermore, in some patients with LM CAD, exercise myocardial perfusion imaging may not show any transient or fixed myocardial perfusion abnormalities due to balanced ischaemia.\textsuperscript{12} Most of these patients do have normal wall motion at rest and it will be beneficial if another resting parameter can distinguish severe CAD from less severe CAD. Thus, a subtle PLSL reduction in patients with LM or three-vessel CAD may provide an important diagnostic clue and allow
stress testing to be performed more safely and provide a higher pretest probability for the presence of high-risk CAD. The 2D strain with the speckle tracking method was recently developed for the quantitative evaluation of LV systolic function. Moreover, this method has been validated for the evaluation of longitudinal LV function. In the present study, we used a semi-automated algorithm of AFI technique, which allows measures of global and segmental PSLS to be made in a routine clinical setting and requires a very little additional time to routine wall motion analysis by visual estimation. In addition to angle independency, the speckle tracking method has some theoretical advantages in terms of measuring strain over the tissue Doppler method. In the latter method, strain values are calculated by integrating strain rate vs. time curves. However, strain is a fundamental parameter of the 2D speckle tracking method, and can be obtained directly by determining relative changes in distances between two points of nearby traced myocardium. Moreover, segmental analysis provides a more intuitive bull's eye display, generated by the AFI

Figure 2  Comparison of global and segmental peak systolic longitudinal strains (PSLS) by study group using one-way analysis of variance with post hoc analysis with Bonferroni’s correction. Global and segmental PSLSs were greater in the normal group than in the high-risk group, but no significant difference was noted between groups regarding left ventricular ejection fraction (LV EF). PSLSs are presented as absolute values.

Figure 3  Receiver operating characteristic (ROC) curve analysis for prediction of high-risk CAD defined as three-vessel disease or left main disease. CAD, coronary artery disease; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; PSLS, peak systolic longitudinal strain.
technique, and enables quantitative analysis of LV long-axis function.

In the present study, PSLSs of mid- and basal LV segments were significantly lower than those of the apical segment. Apex of LV has prominent rotational movement in addition to longitudinal and short-axis motion, and this might result in the incorrect estimation of longitudinal function in this segment. Moreover, inner myocardium, which is known to be most susceptible to myocardial ischaemia, and which is the major component responsible for long-axis function, has a helical fibre orientation. This helical structure might result in parallel alignment of longitudinal axis and inner myocardium only in the LV mid or basal. Apical myocardium is rather aligned in a circular direction, which might be associated with short-axis function or rotational movement.

There are some limitations in our study. First, a relatively small numbers of patients were enrolled. Second, selection bias is possible since our study was performed in a tertiary centre where evaluations were performed in a referral base. Third, the patients with significant CAD had medications such as β-blocker, angiotensin-converting enzyme inhibitor, and angiotensin II receptor antagonist more frequently. As PSLSs were known to be influenced by loading condition, these medications might have some effect on the PSLS values. However, the differences of PSLS especially in the mid- and basal segments between the high- and low-risk groups were evident although the use of these drugs was similar in these two groups. Forth, we did not evaluate LM CAD using intravascular ultrasound or functional studies (e.g. fractional flow reserve), which might have provided a more accurate measure of degree of stenosis or myocardial ischaemia, especially in patients with LM CAD. We did not evaluate strain rate, which could not be obtained directly from AFI software. However, as PSLS is a primary parameter that can be directly calculated via the speckle tracking method, strain might be a more relevant parameter than tissue Doppler study. Finally, the reduction in PSLS may not be specific to severe CADs and may be present in other myopathic conditions and further clinical investigations will be necessary to validate our observations.

Conclusions

The present study showed that resting PSLS is significantly reduced in patients with severe CAD including LM or three-vessel CAD, even when resting wall motion and LV ejection fraction are normal. Therefore, PSLS measured by 2D strain with AFI technique may be a more sensitive marker than wall motion abnormality for severe ischaemic heart disease.

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Conflict of interest: none declared.

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