Coronary Artery Disease

Myocardial Strain Analysis by 2-Dimensional Speckle Tracking Echocardiography Improves Diagnostics of Coronary Artery Stenosis in Stable Angina Pectoris

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Background—Two-dimensional strain echocardiography detects early signs of left ventricular dysfunction; however, it is unknown whether myocardial strain analysis at rest in patients with suspected stable angina pectoris predicts the presence of coronary artery disease (CAD).

Methods and Results—In total, 296 consecutive patients with clinically suspected stable angina pectoris, no previous cardiac history, and normal left ventricular ejection fraction were included. All patients were examined by 2-dimensional strain echocardiography, exercise ECG, and coronary angiography. Two-dimensional strain echocardiography was performed in the 3 apical projections. Peak regional longitudinal systolic strain was measured in 18 myocardial sites and averaged to provide global longitudinal peak systolic strain. Duke score, including ST-segment depression, chest pain, and exercise capacity, was used as the outcome of the exercise test. Patients with an area stenosis ≥70% in ≥1 epicardial coronary artery were categorized as having significant CAD (n=107). Global longitudinal peak systolic strain was significantly lower in patients with CAD compared with patients without (17.1±2.5% versus 18.8±2.6%; P<0.001) and remained an independent predictor of CAD after multivariable adjustment for baseline data, exercise test, and conventional echocardiography (odds ratio, 1.25 [P=0.016] per 1% decrease). Area under receiver operating characteristic curve for exercise test and global longitudinal peak systolic strain in combination was significantly higher than that for exercise test alone (0.84 versus 0.78; P=0.007). Furthermore, impaired regional longitudinal systolic strain identifies which coronary artery is stenotic.

Conclusions—In patients with suspected stable angina pectoris, global longitudinal peak systolic strain assessed at rest is an independent predictor of significant CAD and significantly improves the diagnostic performance of exercise test. Furthermore, 2-dimensional strain echocardiography seems capable of identifying high-risk patients.

Key Words: coronary artery disease • diagnostic performance • myocardial ischemia • stable angina pectoris • two-dimensional speckle tracking echocardiography • two-dimensional strain echocardiography

Echocardiography is the leading cardiac imaging technique in patients with suspected cardiac disease. However, conventional echocardiography at rest provides little information on the presence of coronary artery disease (CAD) in patients suspected of having stable angina pectoris (SAP). Longitudinally oriented myocardial fibers are located subendocardially, the area most susceptible to ischemia, why measurements of longitudinal motion and deformation may be the most sensitive markers of CAD using tissue Doppler imaging (TDI) or 2-dimensional strain echocardiography (2DSE). However, regional myocardial velocities obtained by TDI have the disadvantage of being influenced by tethering to adjacent segments and heart movement, making 2DSE more suitable for diagnosing impaired segmental longitudinal mechanics caused by CAD. Furthermore, 2DSE can be implemented in the conventional echocardiographic protocol because it is a postprocessing analysis from standardized echocardiographic images. Hence, it would be appealing whether 2DSE could provide additional information on the diagnosis of CAD in patients with SAP.

Clinical Perspective on p 65

Exercise testing is recommended as a first-line diagnostic test in patients with suspected SAP, although the limited sensitivity and specificity have been criticized. Thus, it would be encouraging if 2DSE performed at rest could improve the diagnostic accuracy of the exercise test because both an
echocardiographic examination and an exercise test are recommended as first-line diagnostic tests in patients with suspected SAP.

It is unknown whether 2DSE is able to predict the presence of significant CAD in patients referred with suspected SAP. Therefore, the aim of this study was to determine whether simple 2DSE performed at rest can predict the presence of significant CAD in consecutive patients referred with SAP and improve the diagnostic performance of an exercise test. Furthermore, this study also investigates whether 2DSE is appropriate for diagnosing impairment of the segmental longitudinal mechanics caused by CAD and thereby identify which coronary artery is stenotic.

Methods

Study Population
From September 2008 to March 2011, 296 consecutive patients referred with suspected SAP were included. SAP was defined as chest pain or discomfort (angina) suspected to be caused by myocardial ischemia. Anginal symptoms were considered stable if they had been occurring for several weeks without deterioration and were typically induced by activity or stress. Patients with known ischemic heart disease, congestive heart failure, heart valve disease, left ventricular ejection fraction <50%, intraventricular conduction disturbances, pathological Q waves, and arrhythmias were excluded. All patients were examined with echocardiography, including 2DSE, and exercise test followed by coronary angiography. Coronary angiography was performed, regardless of the outcome of echocardiography and exercise test.

Echocardiography
All echocardiograms were obtained using Vivid 7 Dimension (GE Healthcare; Horten, Norway) with a 3.5-MHz transducer. All individuals were examined using conventional 2-dimensional echocardiography and analyzed off-line using 2-dimensional speckle tracking. All off-line analyses were performed with commercially available software (EchoPAC; GE Healthcare; Horten, Norway) by a blinded investigator.

Conventional Echocardiography
Left ventricular (LV) end-diastolic dimensions (interventricular septal wall thickness, LV internal dimension, and LV posterior wall thickness) were obtained from the parasternal long-axis view at the mitral valve leaflet tips. LV mass index (LVMI) was calculated as the anatomic mass divided by the body surface area. Peak velocity of early (E) and atrial (A) diastolic filling and deceleration time (DT) of the E wave were measured, and the E/A ratio was calculated. LV ejection fraction (LVEF) was determined using the modified biplane Simpson method. Left atrial volume was estimated by the area–length method and divided by the body surface area, creating the left atrial volume index. Pulsed-wave TDI tracings were obtained with the range gate placed at the septal and lateral mitral annular segments in the 4-chamber view. The peak longitudinal early diastolic (e') velocity was measured, and the average was calculated from the lateral and septal velocities and used to obtain E/e'.

Two-Dimensional Strain Echocardiography
2DSE was performed from the apical 4-chamber, 2-chamber, and apical long-axis view (mean, 92 frames/s; SD, 16 frames/s). By speckle tracking, the endocardial border was traced in end systole. The integrity of speckle tracking was automatically detected and visually ascertained. In case of poor tracking, the region of interest tracing was readjusted. Segments with persistent inadequate tracking were excluded from analysis (8% of all segments). Regional longitudinal peak systolic strain (RLS) was measured in all views between aortic valve opening and closing for the 6 basal, 6 midventricular, and 6 apical segments, and averaged from the 18 segments to provide global longitudinal peak systolic strain (GLS). We also calculated the GLS only including the 6 basal and 6 midventricular segments (GLS), thereby excluding the apical segments, as previously recommended. In each segment, peak longitudinal systolic strain rate (SRs), peak longitudinal early diastolic SR, and peak longitudinal late diastolic SR were measured and averaged to provide global estimates, both including all 18 segments and after excluding the 6 apical segments.

Exercise ECG
All patients underwent symptom-limited bicycle exercise testing according to the recommended standard bicycle exercise protocol. Heart rate, blood pressure, and 12-lead ECGs were recorded at rest and every second minute of exercise. The ECGs were analyzed and categorized as either normal or abnormal by 2 blinded investigators. An abnormal exercise ST response was defined as ≥1 mm of horizontal or downsloping ST depression (1 point+80 ms) or ≥1 mm ST-segment elevation. Duke score (DS) is considered to be a strong prognostic and diagnostic index because it combines information on exercise capacity, ECG alterations, and symptoms during the exercise test. The DS was used as the outcome of the exercise test. The equation used for calculating the DS was DS=exercise capacity–(5×ST deviation)–(4×exercise angina score). Exercise angina score had a value of 0 if the patient had no angina during test, 1 if the patient had nonlimiting angina, and 2 if angina was the reason the patient stopped the test. ST deviation was the maximum ST deviation during or after exercise in millimeters.

Coronary Angiography
Coronary angiography was performed by the percutaneous femoral approach. Coronary angiograms were obtained for each coronary vessel in ≥2 projections, and stenoses with ≥70% reduction of the arterial lumen area were considered significant. The analysis of the coronary angiograms was performed visually by an experienced operator who was blinded to the results of the echocardiographic examinations.

Statistical Analysis
In Tables 1 to 3, proportions were compared between groups using the χ2 test and continuous Gaussian distributed variables with the Student t test. Logistic regression was performed to adjust for baseline characteristics (age, sex, diabetes mellitus, angina type, diastolic blood pressure, heart rate, and hypercholesterolemia), exercise test (DS), and conventional echocardiography (LVMI, E/A ratio, DT, and e'; Table 1 in the Data Supplement). Receiver operating characteristic curves were constructed (Figures 1 and 2), and area under curve (AUC) was calculated. The difference in AUC from receiver operating characteristic curves based on nested logistic regression models was tested using the roccomp function. From the receiver operating characteristic curves constructed for GLS, and DS, the optimal cut-off value with the highest sensitivity and specificity for diagnosing CAD was identified.

Multiple linear regression models were constructed, and significant stenosis in the left anterior descending coronary artery (LAD), right coronary artery, or left circumflex coronary artery (LCX) was tested as independent predictors of RLS in each of the 18 segments. We thereby obtained information about which coronary artery with significant stenosis (LAD, LCX, or right coronary artery) predicts a reduction of RLS in each of the 18 segments (Figure I in the Data Supplement).

ANOVA was performed to test whether GLS varied with increasing severity of CAD defined by increasing number of stenotic coronary vessels. Intraobserver and interobserver reproducibility was assessed in 25 randomly selected patients using the Bland–Altman method. All analyses were performed with STATA Statistics/Data analysis, SE 12.0 (StataCorp, TX).
Ethics
The regional Committee on Biomedical Research Ethics (j.no. H-C-2008–044) approved the study, and all patients gave written informed consent.

Results
Of the 296 patients enrolled in the study, 3 patients were excluded because of inadequate quality of the echocardiographic examination for 2DSE. Of the remaining 293 patients, 107 had significant CAD, whereas 186 had nonsignificant or no CAD.

Table 1 presents the baseline characteristics. Table 2 presents results from the exercise test. The exercise performance of patients with CAD was impaired in every aspect of the test. Exercise capacity, ST deviation, angina during test, and composite index of all these parameters in terms of the DS were all reduced in patients with CAD. Table 3 presents echocardiographic measures. LVMI was found to be significantly higher, and diastolic measures in terms of reduced E, reduced E/A ratio, prolonged DT, and reduced e’ were all impaired in patients with significant CAD.

GLS, SRs, and global peak longitudinal early diastolic SR obtained from all 18 segments and GLS and global peak longitudinal early diastolic SR obtained from only the 6 basal and 6 midventricular segments (12 segments) were significantly lower in patients with CAD. Only e’ and GLS (both GLS_{18} and GLS_{12}) remained significantly affected after adjustment for baseline characteristics (marked * in Table 3 and displayed in Table I in the Data Supplement).

Notably, after multivariable adjustment for baseline characteristics (age, sex, diabetes mellitus, and angina type), exercise test (DS), and conventional echocardiography (LVMI, E/A ratio, DT, and e’), GLS (both GLS_{18} and GLS_{12}) were the only echocardiographic measures that remained independent predictors of CAD (marked † in Table 3 and displayed in Table I in the Data Supplement).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients Without Significant CAD</th>
<th>Patients With Significant CAD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>186</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>59.2±9.7</td>
<td>63.7±9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>66 (35%)</td>
<td>80 (75%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±11</td>
<td>69±11</td>
<td>0.87</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81±10</td>
<td>80±11</td>
<td>0.35</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1±4.3</td>
<td>26.9±4.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>86 (46%)</td>
<td>58 (54%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>18 (10%)</td>
<td>21 (20%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Nitrates, n (%)</td>
<td>16 (9%)</td>
<td>9 (8%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Platelet inhibitors, n (%)</td>
<td>27 (15%)</td>
<td>23 (22%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Anticoagulant therapy, n (%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0.19</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>29 (16%)</td>
<td>20 (19%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>32 (17%)</td>
<td>19 (18%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>38 (20%)</td>
<td>25 (23%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Previous</td>
<td>72 (39%)</td>
<td>44 (41%)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>63 (34%)</td>
<td>43 (40%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>95 (51%)</td>
<td>43 (40%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>67 (36%)</td>
<td>85 (79%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atypical</td>
<td>77 (41%)</td>
<td>15 (14%)</td>
<td></td>
</tr>
<tr>
<td>Nonanginal chest pain</td>
<td>42 (23%)</td>
<td>7 (7%)</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>...</td>
<td>46 (43%)</td>
<td>...</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>...</td>
<td>28 (26%)</td>
<td>...</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>...</td>
<td>33 (31%)</td>
<td>...</td>
</tr>
<tr>
<td>LAD stenosis</td>
<td>...</td>
<td>77 (72%)</td>
<td>...</td>
</tr>
<tr>
<td>LCX stenosis</td>
<td>...</td>
<td>60 (56%)</td>
<td>...</td>
</tr>
<tr>
<td>RCA stenosis</td>
<td>...</td>
<td>64 (60%)</td>
<td>...</td>
</tr>
<tr>
<td>LM stenosis</td>
<td>...</td>
<td>12 (11%)</td>
<td>...</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean±SD, and categorical data are presented as number (percentage). BMI indicates body mass index; CAD, coronary artery disease; LAD, left anterior descending; LCX, left circumflex coronary artery; LM, left main stenosis; and RCA, right coronary artery.
(1.00–1.41; \(P=0.047\)) per 1% decrease and GLS_{12}: odds ratio, 1.25 (1.04–1.50; \(P=0.016\)) per 1% decrease. Furthermore, when adding diastolic blood pressure, hypercholesterolemia, and heart rate to the multivariable model, only GLS_{12} remained an independent predictor—GLS_{18}: odds ratio, 1.17 (0.98–1.39; \(P=0.08\)) per 1% decrease and GLS_{12}: odds ratio, 1.24 (1.03–1.49; \(P=0.025\)) per 1% decrease (Table I in the Data Supplement).

### Diagnostic Performance of GLS

The diagnostic performance was not significantly different for GLS_{12} and GLS_{18}, determined by the AUCs (GLS_{12}: 0.68 [0.62–0.74]; GLS_{18}: 0.67 [0.60–0.73]). However, only GLS_{12} remained an independent predictor of CAD after multivariable adjustment (also including diastolic blood pressure, hypercholesterolemia, and heart rate) and was, therefore, used for the succeeding analysis.

The diagnostic performance of the exercise test was significantly improved by GLS_{12} in terms of a significant increased AUC for the exercise test in combination with GLS_{12} compared with the exercise test alone (0.84 [0.79–0.88] versus 0.78 [0.72–0.84]; \(P=0.007\); Figure 1). In addition, when adding GLS_{12} to the combination of exercise test and all other echocardiographic predictors of CAD (LVMI, E/A ratio, DT, and \(e'\)), the diagnostic performance was also significantly improved in terms of a significantly increased AUC (0.87 [0.83–0.92] versus 0.85 [0.80–0.90]; \(P=0.034\); Figure 2). Adding all other echocardiographic predictors of CAD (LVMI, E/A ratio, DT, and \(e'\)) to the combination of exercise test and GLS_{12}, conventional echocardiography did not improve the diagnostic performance further (\(P=0.06\)).

The optimal cutoff value for GLS_{12} with the highest sensitivity and specificity for diagnosing CAD was found to be −18.4%, with a sensitivity of 0.74 and a specificity of 0.58. The optimal cutoff value for the DS was found to be 2.13 with a sensitivity of 0.70 and a specificity of 0.74. When combining the 2 cutoff values of GLS_{12} and DS, only 18 patients (9.7%) without CAD had a GLS_{12} <18.4% and a DS <2.13, corresponding to a specificity of 90.3%. Furthermore, the risk of having significant CAD when GLS_{12} was <18.4% and DS was <2.13 was 75% (positive predictive value).

### Significant Coronary Artery Stenosis and Segmental RLS

The segmental RLS was significantly lower in segments supplied by stenotic coronary arteries compared with nonstenotic coronary arteries in a pattern closely mimicking the anatomic perfusion area (Figure I in the Data Supplement). Thus, it is possible to determine which coronary artery is stenotic.

### Table 2. Electrocardiographic Exercise Testing

<table>
<thead>
<tr>
<th>Patients Without Significant CAD</th>
<th>Patients With Significant CAD</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>186</td>
<td>107</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>7.1±1.9</td>
<td>6.3±1.7</td>
</tr>
<tr>
<td>(METs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST deviation (&gt;1) mm</td>
<td>41 (22%)</td>
<td>61 (57%)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurred</td>
<td>49 (26%)</td>
<td>39 (36%)</td>
</tr>
<tr>
<td>Stopped the test</td>
<td>1 (0.5%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Duke score</td>
<td>4.5±3.7</td>
<td>2.0±7.3</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean±SD, and categorical data are presented as number (percentage). Duke score=exercise capacity−(5×ST deviation)−(4×angina score). CAD indicates coronary artery disease; and METs, metabolic equivalents.
Usefulness of 2DSE in Identifying High-Risk Patients

Patients with significant left main (LM) stem stenosis (≥70%) had significantly higher apical longitudinal strain (ALS) compared with patients with significant LAD and LCX stenosis (−19.8±2.4 versus −17.0±3.9; P=0.012), despite similar low GLS12 (−17.1±2.0 versus −16.8±2.5; P=0.73; Figure II in the Data Supplement). We therefore defined a pattern determined by low GLS12 (<18.4%) and high ALS (>18.5%) for identifying the presence of LM stenosis. The absence of a low GLS12 and high ALS could, with 93% (negative predictive value) certainty, rule out the presence of LM stenosis in patients with significant LAD and LCX stenosis (corresponding to a positive predictive value of 33%, specificity of 82%, and sensitivity of 58%). Similar high negative predictive values for diagnosing LM stenosis were found, regardless of investigating the presence of this pattern in the whole population (98%) or only including patients with significant CAD (94%).

Reproducibility of Strain Measures

The Bland–Altman analysis demonstrated a good intraobserver and interobserver agreement for both GLS18 and GLS12, with a small bias. The mean difference ±1.96 SDs was 0.1±1.6% for GLS18 and −0.0±2.1% for GLS12 in the intraobserver analysis and 0.7±2.0% for GLS18 and −0.2±2.0% for GLS12 in the interobserver analysis. The intraobserver and interobserver analysis of the segmental RLS showed reasonable reproducibility for the basal and midventricular segments and less reasonable reproducibility for the apical segments (Figure III in the Data Supplement).

Discussion

Subclinical impairment of the LV has been demonstrated by 2DSE in the setting of many disorders, including hypertension,14 diabetes mellitus,15,16 atrial fibrillation,17 and heart failure, with preserved ejection fraction.18 Smaller previous studies have also demonstrated impaired peak longitudinal strain and SR in patients with CAD.3–6 In the present study, we demonstrated for the first time that postprocessing 2DSE
performed at rest was able to predict CAD in patients enrolled consecutively with suspected SAP. These findings were independent of baseline characteristics, exercise test, and all other conventional echocardiographic predictors (Table I in the Data Supplement). Furthermore, GLS provided incremental value compared with conventional echocardiography and exercise test in diagnosing significant CAD (Figures 1 and 2). In addition, segments supplied by stenotic vessels had impaired RLS (Figure I in the Data Supplement). Finally, the combination of GLS and ALS was able to rule out or identify patients at high risk (Figure 3 and Figure II in the Data Supplement).

The myocardial fibers most susceptible to ischemia are the longitudinally orientated fibers that are located subendocardially. Measurements of longitudinal motion and deformation are therefore the most sensitive markers of CAD. We previously demonstrated that color TDI are sensitive markers of longitudinal dysfunction caused by CAD and that these TDI velocities can improve the diagnostics of CAD in patients suspected of SAP. However, local myocardial velocities obtained by TDI have the disadvantage of being influenced by heart movement and tethering to adjacent segments, which makes 2DSE more suitable for diagnosing impaired segmental longitudinal mechanics caused by CAD. Furthermore, in our study, GLS had higher AUC for diagnosing CAD compared with TDI velocities.

Patients enrolled had no previous history of cardiac disease, prevalence of cardiac risk factors was relatively low, and conventional echocardiography was normal, determined by LVEF. Accordingly, overall prevalence of disease was low (prevalence of CAD was 37%). The fact that GLS performed at rest was an independent predictor of CAD even in a low-risk population implies that GLS might be useful for risk stratification of patients with suspected SAP. In addition, GLS at rest improved the diagnostic power of exercise test (Figure 1). Exercise test is recommended as a first-line diagnostic test in patients with suspected SAP, despite its limited sensitivity and specificity. Hence, it is encouraging that 2DSE might improve the diagnostic accuracy of the exercise test.

A cutoff of GLS >18.4% may seem high compared with the normal range described in the HUNT study. However, in the HUNT study, 2DSE was performed using customized semiautomatic software that is not commercially available. We used the commercial available EchoPac software for our analysis, and a previous comparison between the 2 software demonstrated that the EchoPac software systematically measures higher strain values (≈1% higher strain) compared with their customized software.

Both 2DSE and some conventional echocardiographic measures were affected in patients with CAD compared with patients without CAD (Table 3). Still, GLS was the strongest predictor of CAD because only GLS remained an independent predictor of significant CAD after adjustment for all other predictors in our population (Table I in the Data Supplement). Furthermore, GLS improved the diagnostic performance of exercise test in combination with all other conventional echocardiographic measures (Figure 2). In contrast, conventional echocardiography did not improve the diagnostic performance of exercise test and GLS in combination. Thus, if an evaluation of GLS is added to the results of the exercise test, addition of any other echocardiographic parameter does not seem to improve the diagnostics of significant CAD in patients with suspected SAP.

A previous smaller study investigated the diagnostic use of 2DSE in patients with suspected SAP. However, only the usefulness of the segmental strain and SR measures, not global estimates, was assessed in ischemic and nonischemic segments, respectively. Ischemic segments were assigned to a prespecified vascular territory. The same approach was used in a study investigating the usefulness of 2DSE in patients admitted to the emergency department with chest pain. In contrast, in our study, ischemic segments were not assigned to prespecified vascular territories because we obtained information about how significant stenosis in LAD, right coronary artery, or LCX, respectively, affects RLS in each segment (Figure I in the Data Supplement). This was done by performing multiple linear regression models, including significant stenosis in LAD, right coronary artery, and LCX as independent predictors of RLS in each of the 18 segments. A pattern closely mimicking the prespecified vascular territory appeared. Nevertheless, RLS in some segments was affected by significant stenosis in other coronary arteries than expected by the prespecified territory (Figure I in the Data Supplement). Therefore, if a patient admitted for suspected SAP has a normal conventional echocardiography and demonstrates a low GLS at rest, the suspicion about the presence of significant CAD should be evoked. This suspicion should be amplified if the RLS shows low values in ≥1 of the vascular territories illustrated in Figure IA in the Data Supplement. Liang et al reported systolic and early diastolic SR to be the strongest predictors of significant CAD. This is in contrast to our results in which neither the systolic nor the early diastolic SR remained independent predictors of CAD when adjusting for baseline variables.

In addition, 2DSE seemed to be able to rule out or identify patients at high risk, determined by the presence of LM stenosis or multivessel disease (Figure 3 and Figure II in the Data Supplement). Revascularization in these high-risk patients has been proven to improve prognosis. GLS declined incrementally with increasing severity of CAD defined by increasing number of stenotic coronary vessels. Therefore,
the risk of multivessel disease increases with decreasing GLS$_{12}$. If a patient suspected of CAD demonstrates a low GLS$_{12}$ and low segmental RLS in the vascular territories of LAD and LCX but lacks the high ALS pattern, the risk of an LM stenosis and, therefore, an adverse prognosis is low. The basal myocardial segments seem more affected by proximal coronary stenosis, which are known to be the most dangerous. The pattern identifying patients with LM stenosis has actually been discovered in a previous study; however, the authors described the low GLS$_{12}$ and high ALS pattern found in patients with LM stenosis as a weakness in using the apical segments in identifying high-risk patients. As opposed to the later conclusion, we find this pattern to be a necessity but not a specific marker of LM stenosis because the absence of the pattern will rule out the presence of significant LM stenosis. Despite preserved LVEF, longitudinal systolic function of the LV in terms of GLS proved to be impaired among patients with CAD. Previous studies have demonstrated a similarly early impairment of the longitudinal systolic function in patients with CAD and preserved regional wall motion in addition to a normal LVEF. However, the previous studies on predictive power of 2DSE have included patients with various types of CAD ranging from patients admitted with acute coronary syndrome to patients without chest pain but in high risk of CAD determined from their Duke clinical score. None of the previous studies have included an exercise test in the diagnostic workup. This makes our population more homogeneous, less confounded by difference in phenotype, and mimics the challenging clinical setting better.

Limitations
LV wall motion abnormalities may be because of other conditions than ischemia, such as age, sex, hypertension, diabetes mellitus, heart valve disease, or intraventricular conduction disturbance. However, to avoid confounding from these conditions, patients with heart valve disease or intraventricular conduction disturbance were excluded, and adjusted analyses were performed for significant confounders.

Wall motion score index was not determined in the present study. However, because the patients enrolled had no prior history of cardiac disease, prevalence of cardiac risk factors was relatively low, and conventional echocardiography was normal, determined by a normal LVEF, we do not think that visually impaired wall motion abnormalities would be frequent. The strength of strain analysis is that it is an objective measure able to detect miniscule changes in longitudinal performance on a continuous scale. In contrast, the wall motion score index is a visually attained subjective measure with limited numbers of categories, which might explain why miniscule changes in longitudinal performance may not be detected.

Although the patients were enrolled consecutively, selection may have occurred. Only patients without a history of heart disease, patients with a normal LVEF, and patients with a normal resting ECG were enrolled. Hence, the patients enrolled in the present study may have a relatively low risk of CAD. Despite this limitation, 2DSE performed at rest was found to be an independent predictor of CAD, and 2DSE would probably be an even stronger predictor in patients with higher risk of CAD.

Radial, transverse, circumferential strain and synchrony analysis were not performed in the present study. However, the myocardial fibers most susceptible to ischemia are the longitudinally orientated fibers that are located subendocardially, why measurements of longitudinal deformation are thought to be the most sensitive markers of CAD.

Our analyses did not include an independent validation group, why our results need to be validated in other SAP populations. Furthermore, we did not adjust for multiple tests among the large number of statistical comparisons presented in tables and figures, why the potential increased rate in the experimental-wise type I error should be taken into account.

Conclusions
In patients with suspected SAP, GLS assessed by 2DSE at rest is an independent predictor of significant CAD and significantly improves the diagnostic performance of exercise test. Furthermore, 2DSE seems capable of identifying high-risk patients.

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Disclosures
None.

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CLINICAL PERSPECTIVE

Both acute and chronic ischemia decrease regional wall motion and deformation. In chronic ischemia, it has been demonstrated that recurrent ischemia and stunning can lead to structural changes such as fibrosis and loss of myocytes. However, despite these significant changes in segmental contractile function, conventional measures of left ventricular contractile function may be unaffected. Furthermore, this impairment in longitudinal systolic function is known to be compensated by augmentation of circumferential deformation, which might explain why the left ventricular ejection fraction is preserved, despite impaired longitudinal systolic function. The myocardial fibers most susceptible to ischemia are the longitudinally oriented fibers that are located subendocardially. Measurements of longitudinal motion and deformation are, therefore, the most sensitive markers of coronary artery disease. In the present study, we found that postprocessing 2-dimensional strain echocardiography performed at rest was able to predict coronary artery disease in patients enrolled consecutively with susceptible stable angina pectoris. Furthermore, these findings were independent of baseline characteristics, exercise test, and all other conventional echocardiographic predictors. Furthermore, global longitudinal peak systolic strain provided incremental value compared with conventional echocardiography and exercise testing in diagnosing significant coronary artery disease. The present study provides the clinician with a cutoff value of global longitudinal peak systolic strain, with highest sensitivity and specificity for diagnosing coronary artery disease, by which the suspicion for the presence of significant coronary artery disease should be evoked. Furthermore, 2-dimensional strain echocardiography seems capable of identifying patients at high risk, as determined by the presence of multivessel disease or left main stem stenosis.
Myocardial Strain Analysis by 2-Dimensional Speckle Tracking Echocardiography Improves Diagnostics of Coronary Artery Stenosis in Stable Angina Pectoris
Tor Biering-Sørensen, Soren Hoffmann, Rasmus Mogelvang, Allan Zeeberg Iversen, Søren Galatius, Thomas Fritz-Hansen, Jan Bech and Jan Skov Jensen

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SUPPLEMENTAL MATERIAL

Figure Legends

Figure S1: Title: Significant coronary artery stenosis and segmental RLS.
Caption: Figure S1a: RLS in segments supplied by coronary arteries with significant coronary artery stenosis compared to RLS in patients without significant coronary artery stenosis in the respective coronary arteries. Multiple linear regression models were constructed and significant stenosis in the LAD, RCA and LCX were tested as independent predictors of RLS in each of the 18 segments.

Figure S1b: The typical perfusion distributions of the RCA, the LAD, and the LCX1
RLS=Regional longitudinal peak systolic strain; LAD=Left anterior descending; RCA=Right coronary artery; LCX = Left circumflex coronary artery; ANT=Anterior; LAT=Lateral; POST=Posterior; INF=Inferior; SEPT=Septal; ANT SEPT=Anterior septal.

Figure S2: Title: RLS in patients with LM stenosis compared to patients with LAD and LCX stenosis.
Caption: Segmental RLS in patients with significant LM stenosis compared to patients with significant LAD and LCX stenosis.
RLS=Regional longitudinal peak systolic strain; LM=Left main stenosis; LAD=Left anterior descending; LCX=Left circumflex coronary artery; ANT=Anterior; LAT=Lateral; POST=Posterior; INF=Inferior; SEPT=Septal; ANT SEPT=Anterior septal.
Figure S3: Title: Intra- and interobserver reproducibility for the RLS. Caption: Bland-Altman analysis displaying the mean difference ± 1.96 SDs for each segment. Intra- (Figure S3a) and interobserver (Figure S3b) differences of the RLS showing mean difference and 95% limits of agreement. 

RLS=Regional longitudinal peak systolic strain; ANT=Anterior; LAT=Lateral; POST=Posterior; INF=Inferior; SEPT=Septal; ANT SEPT=Anterior septal.
Figure S2
Figure S3b

Interobserver variability

ANT

LAT

ANT SEPT

SEPT

POST

INF

LAD

CX

RCA

1.2 ± 4.4%
-0.5 ± 4.4%
-4.1 ± 8.5%
-2.4 ± 7.3%
-1.1 ± 4.6%
0.5 ± 2.0%
-2.6 ± 7.1%
-0.3 ± 4.2%
0.6 ± 4.0%
-0.8 ± 3.7%
-4.1 ± 8.5%
-1.3 ± 4.7%
-1.7 ± 6.1%
0.1 ± 2.7%
-0.8 ± 3.2%
0.2 ± 2.5%
#### Table S1

**Independent echocardiographic predictors of coronary artery disease**

<table>
<thead>
<tr>
<th>Models including GLS\textsubscript{18}:</th>
<th>Univariable</th>
<th>Model 1: Including age, gender, DM and angina type + one of each echocardiographic variable listed below</th>
<th>Model 2: Including age, gender, DM, angina type and duke score + all of the echocardiographic variables listed below</th>
<th>Model 3: Including age, gender, DM, angina type, duke score, diastolic BP, hypercholesterolemia, HR + all of the echocardiographic variable listed below</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI per 1 g/m\textsuperscript{2} increase</td>
<td>1.04 (1.02-1.06) \textit{&lt;0.001}</td>
<td>1.02 (1.00-1.04) \textit{0.07}</td>
<td>1.02 (1.00-1.04) \textit{0.12}</td>
<td>1.02 (1.00-1.05) \textit{0.07}</td>
</tr>
<tr>
<td>E/A ratio per 1 increase</td>
<td>0.15 (0.05-0.41) \textit{&lt;0.001}</td>
<td>0.32 (0.09-1.17) \textit{0.09}</td>
<td>0.45 (0.07-2.99) \textit{0.41}</td>
<td>0.65 (0.08-5.53) \textit{0.69}</td>
</tr>
<tr>
<td>DT per 1 ms increase</td>
<td>1.01 (1.00-1.01) \textit{0.017}</td>
<td>1.01 (1.00-1.01) \textit{0.10}</td>
<td>1.00 (0.99-1.01) \textit{0.93}</td>
<td>1.00 (0.99-1.01) \textit{0.97}</td>
</tr>
<tr>
<td>e' per 1 cm/s decrease</td>
<td>1.34 (1.16-1.54) \textit{&lt;0.001}</td>
<td>1.26 (1.04-1.52) \textit{0.017}</td>
<td>1.19 (0.89-1.58) \textit{0.24}</td>
<td>1.23 (0.91-1.65) \textit{0.18}</td>
</tr>
<tr>
<td>GLS\textsubscript{18} per 1% decrease</td>
<td>1.27 (1.15-1.40) \textit{&lt;0.001}</td>
<td>1.15 (1.02-1.30) \textit{0.021}</td>
<td>1.19 (1.00-1.41) \textit{0.047}</td>
<td>1.17 (0.98-1.39) \textit{0.08}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Models including GLS\textsubscript{12}:</th>
<th>Univariable</th>
<th>Model 1: Including age, gender, DM and angina type + one of each echocardiographic variable listed below</th>
<th>Model 2: Including age, gender, DM, angina type and duke score + all of the echocardiographic variables listed below</th>
<th>Model 3: Including age, gender, DM, angina type, duke score, diastolic BP, hypercholesterolemia, HR + all of the echocardiographic variable listed below</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI per 1 g/m\textsuperscript{2} increase</td>
<td>1.04 (1.02-1.06) \textit{&lt;0.001}</td>
<td>1.02 (1.00-1.04) \textit{0.07}</td>
<td>1.02 (0.99-1.04) \textit{0.13}</td>
<td>1.02 (1.00-1.05) \textit{0.07}</td>
</tr>
<tr>
<td>E/A ratio per 1 increase</td>
<td>0.15 (0.05-0.41) \textit{&lt;0.001}</td>
<td>0.32 (0.09-1.17) \textit{0.09}</td>
<td>0.51 (0.08-3.49) \textit{0.50}</td>
<td>0.72 (0.08-6.28) \textit{0.76}</td>
</tr>
<tr>
<td>DT per 1 ms increase</td>
<td>1.01 (1.00-1.01) \textit{0.017}</td>
<td>1.01 (1.00-1.01) \textit{0.10}</td>
<td>1.00 (0.99-1.01) \textit{0.91}</td>
<td>1.00 (0.99-1.01) \textit{0.85}</td>
</tr>
<tr>
<td>e' per 1 cm/s decrease</td>
<td>1.34 (1.16-1.54) \textit{&lt;0.001}</td>
<td>1.26 (1.04-1.52) \textit{0.017}</td>
<td>1.13 (0.84-1.53) \textit{0.41}</td>
<td>1.17 (0.87-1.59) \textit{0.30}</td>
</tr>
<tr>
<td>GLS\textsubscript{12} per 1% decrease</td>
<td>1.29 (1.15-1.40) \textit{&lt;0.001}</td>
<td>1.18 (1.04-1.34) \textit{0.008}</td>
<td>1.25 (1.04-1.50) \textit{0.016}</td>
<td>1.24 (1.03-1.49) \textit{0.025}</td>
</tr>
</tbody>
</table>
DM=Diabetes, BP=Blood Pressure, HR=Heart Rate, LVMI=Left Ventricular Mass Index, E=peak transmitral early diastolic inflow velocity, A=peak transmitral late diastolic inflow velocity, DT=decelerations time of early diastolic transmitral inflow, e’=average peak early diastolic longitudinal mitral annular velocity obtained from the septal and lateral myocardial segment, GLS=Global longitudinal peak systolic strain.
References