Incremental Value of Strain Rate Imaging to Wall Motion Analysis for Prediction of Outcome in Patients Undergoing Dobutamine Stress Echocardiography

Charlotte Bjork Ingul, MD; Ellen Rozis, MD; Stig A. Slordahl, PhD; Thomas H. Marwick, MD, PhD

Background—Wall motion score at dobutamine stress echocardiography is an independent predictor of mortality. We sought to determine whether quantification of DSE by strain rate imaging was incremental to wall motion score for predicting outcome.

Methods and Results—In 646 patients undergoing dobutamine stress echocardiography for the evaluation of known or suspected coronary disease, customized software was used to automatically measure peak systolic strain rate (SRs) and end-systolic strain (Ses) in 18 segments. Results were expressed as the number of abnormal segments and the mean SRs and Ses per patient. All-cause mortality was identified over 7 years of follow-up (mean, 5.2±1.5 years). Contributions of clinical, wall motion, and SRs and Ses data to outcome were analyzed with Cox models, which also were used to define cut points for SRs and Ses. Ischemia (new or worsening wall motion abnormalities) was detected in 45%, and 39% had a previous myocardial infarction. In patients with no ischemia, annualized mortality without and with previous myocardial infarction were 2% and 3% compared with 5% in patients with ischemia. Peak wall motion score index, mean SRs, segmental Ses, and segmental SRs were all predictors of mortality, but only segmental SRs (hazard ratio, 3.6; 95% CI, 1.7 to 7.2) was independently predictive. In sequential Cox models, the model based on clinical data (overall χ², 18.4, P=0.002) was improved by peak wall motion score index (31.8, P<0.001) or mean SRs (25.7, P=0.009).

Conclusions—Segmental analysis by SRs, derived from automated strain rate imaging analysis of dobutamine stress echocardiography response, offers prognostic information that is independent and incremental to standard wall motion score index. (Circulation. 2007;115:1252-1259.)

Key Words: echocardiography • prognosis • stress

A

A normal wall motion (WM) at dobutamine stress echocardiography (DSE) is an independent predictor of mortality in patients with known or suspected coronary artery disease (CAD), and risk increases in parallel with the extent of WM abnormality.1,2 Although DSE is used widely to assess CAD, its interpretation is demanding, and its accuracy depends on the experience and training of the reader.3 Despite technical advances and digital image processing and display, both its reproducibility and accuracy are dependent on image quality. DSE also is limited by its relative insensitivity for mild single-vessel disease, low sensitivity for recognizing the presence of multivessel coronary disease, and difficulty in detection of ischemia within areas of abnormal resting WM. A more objective technique could overcome many of these limitations.

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Quantification of DSE with tissue Doppler is less dependent on 2-dimensional image quality than quantification from 2-dimensional echocardiography, and several studies have shown the technique to be feasible for DSE using either velocity or strain rate imaging (SRI).4–6 SR and strain can characterize regional myocardial deformation at rest and can quantify normal or abnormal regional function during DSE.5,7,8 These results may be compromised by many pitfalls, however, including reverberations, misalignment, and angulation. Indeed, none of the tissue Doppler–derived parameters are completely objective because the region of interest is set manually and therefore may be colored by the assessment of WM. To objectively analyze regional myocardial function on the basis of tissue Doppler, we have developed a quick and feasible automated SRI method that includes tracking the region of interest laterally by using the speckle pattern and axially by tissue Doppler.9 In the tissue Doppler method, SR is derived from the velocity gradient of 2 points at a fixed distance along the ultrasound beam, and strain is measured by the temporal integration of SR. The automated method for
TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (fasting glucose &gt;7 mmol/L)</td>
<td>127 (20)</td>
</tr>
<tr>
<td>Hypertension (BP &gt;140/90 mm Hg)</td>
<td>330 (52)</td>
</tr>
<tr>
<td>Hypercholesterolemia (total cholesterol &gt;4 mmol/L)</td>
<td>324 (51)</td>
</tr>
<tr>
<td>Smoking</td>
<td>148 (23)</td>
</tr>
<tr>
<td>Past cardiac history</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>251 (39)</td>
</tr>
<tr>
<td>Angina</td>
<td>294 (46)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>67 (10)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>60 (9)</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>256 (40)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>203 (32)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>157 (24)</td>
</tr>
<tr>
<td>Weight, kg, mean ± SD</td>
<td>78 ± 18</td>
</tr>
<tr>
<td>Height, cm, mean ± SD</td>
<td>169 ± 14</td>
</tr>
</tbody>
</table>

Values are n (%) when appropriate. BM indicates blood pressure; PTCA, percutaneous coronary angioplasty; and CABG, coronary artery bypass grafting.

Echocardiographic Acquisition

Cine loops from LV apical views (4-chamber, 2-chamber, and long-axis views) were recorded simultaneously in both tissue second-harmonic mode and tissue Doppler mode (Vivid 5; GE Vingmed Ultrasound, Horten, Norway). Images were recorded at baseline, low dose, peak, and recovery in a digitized quad-screen format. The pulse repetition frequency was between 1 and 1.5 kHz, and the frame rate (both for tissue Doppler and B-mode) ranged from 75 to 133 per second (median, 90). The number of samples along the beam ranged from 102 to 258 (median, 150) for tissue Doppler and 188 to 486 (median, 420) for B-mode imaging. The number of beams ranged from 10 to 28 (median, 16) for tissue Doppler and from 20 to 87 (median, 41) for B-mode imaging. Echo data were stored digitally for subsequent offline analysis.

Echocardiographic Analysis

Two dimensional gray-scale echo images, interpreted by an experienced observer, were scored as normal (score=1), hypokinetic (2), severely hypokinetic (2.5), akinetic (3), or dyskinetic (4). Infarction was recognized on the basis of severe hypokinesis, akinesis, or dyskinesis at rest. Ischemia was identified in the presence of new or worsening WM abnormality in ≥1 segments during DSE, and a study was identified as abnormal if there were scarred segments with or without ischemia. WM score index (WMSI), number of ischemic segments, and number of scarred segments also were compared. A negative study was characterized by a normal response in all segments.

SRI Analysis

Automated measurements of SRI variables used a Matlab-based (MathWorks Inc, Natick, Mass) custom-made program described earlier by our group. All SRI measurements were obtained by a single observer blinded to all results (clinical and WM). Segments were tracked according to position, orientation, and length throughout the cycle, axially (along the ultrasound beam) by tissue Doppler data, and laterally by speckle tracking. The difference in acquisition time for B-mode and tissue Doppler imaging data was taken into account and compensated for by temporal interpolation in the speckle tracking algorithm. The segment was discarded if the speckle pattern region failed to track properly or if the gray-scale image showed regions with missing ultrasound data (dropsouts) or large reverberations. The displacement of the kernel region was used to check the tracking; ideally, this should be 0 because the kernel returns to the same baseline position by the end of the cardiac cycle. A displacement >2 mm indicated poor tracking.

The timing of aortic valve closure was defined automatically with tissue Doppler imaging. For the purposes of the present study, SRI parameters were measured using velocity data. This method involved automatic placement of a region of interest in the center of the basal and mid segments at end diastole and the basal part of the apical segments to limit the effects of angulation toward the apex. The segment was tracked throughout the cardiac cycle as described. Longitudinal SR was calculated from the velocity gradient along the ultrasound beam, and strain was calculated as the temporal integral of SR from corrected from Eulerian SR to Lagrangian strain, both angle

Stress Protocol

After a resting echocardiogram was obtained, a standard DSE protocol was performed with incremental dobutamine infusion rates of 5, 10, 20, 30, and 40 μg·kg⁻¹·min⁻¹ every 3 minutes. Patients who did not achieve 85% of the age-predicted maximal heart rate (220−age) were given atropine in 0.3-mg increments up to 1.2 mg until target heart rate was achieved. Cardiac rhythm and blood pressure were monitored before and during the test. The stress test was terminated because of completion of the protocol, severe ischemia (severe angina, extensive new WM abnormalities, horizon-
value of all segments (mean SR, or mean Ses) or the number of abnormal segments at risk (segmental SR, or segmental Ses). The series were randomly divided, with half of the patients (n=320) used for defining the optimal cut points of patients at low and high risk of mortality with respect to SR, Ses, WMSI, number of ischemic segments, and number of scarred segments. The number of abnormal segments at risk was defined as the number with an SR or Ses below the defined cut points. The remaining patients were used for testing these cut points.

Follow-Up Data
All-cause mortality was the primary end point. Follow-up was obtained by review of the patient’s hospital or family practice chart or telephone interview with the patient or relative. Patients were censored at the time of percutaneous or surgical revascularization.

Statistical Analysis
Categorical variables are expressed as proportions; continuous variables are expressed as mean±SD. ANOVA was used to compare the means between the 4 different groups with or without ischemia and previous MI, with Scheffé post hoc test used for multiple comparisons. Multiple measures per patient were corrected for within a previous MI, with Scheffé post hoc test used for multiple comparisons. Cox models were used to estimate the univariable hazard ratio of event for each variable. The incremental value of SRI variables over WMSI and clinical variables was assessed in a series of Cox models in which the first model consisted of fitting the clinical data entered as a block (diabetes mellitus, previous MI, age) in the test group. Each echo variable (rest and peak WMSI, mean SR, mean Ses, segmental SR, segmental Ses) was then entered into separate models in combination with this clinical block. Model χ² was then compared for each Cox model. Analyses were performed using standard statistical software (SPSS version 12, SPSS, Chicago, Ill), and values of P<0.05 were considered statistically significant.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Dobutamine Echocardiography
Adequate heart rate was achieved in 97% of the patients (n=640). In the remaining 21 patients, the protocol was terminated at a submaximal heart rate because of severe ischemia or side effects (hypotension, hypertension, ventricular arrhythmia, patient intolerance; n=15) or inability to attain target heart rate despite dobutamine and atropine (n=6). The test was nondiagnostic in 6 patients (1%), most commonly because of failure to reach target heart rate. Table 2 summarizes the hemodynamics and stress results for the 640 patients with adequate heart rate response.

A completely normal test at rest and stress was found in 267 patients (42%). Resting WM abnormality was present in 251 patients (39%), and in 87 patients (14%), this was the only abnormality. Ischemia by WM was found in 286 patients (45%); ischemia alone was detected in 122 patients (19%) and ischemia with prior MI in 164 patients (26%). The majority (82%) of patients with ischemia had >1 ischemic segment at peak stress.

A total of 11 520 myocardial segments were analyzed with tissue Doppler. Automated analysis of SR, was possible in 93% of the segments compared with 87% for Ses. WM at peak identified 984 ischemic segments, 356 viable segments, and 979 scarred segments. Patients with a normal response to dobutamine and normal resting WM demonstrated significantly a higher magnitude of mean SR, and mean Ses compared with the patients with ischemia and prior MI (Table 3).
Outcomes and Events During Follow-Up
In total, 107 patients (17%) died during the follow-up period. Myocardial revascularization was performed in 51 patients: 31 had PCI (5%) and 20 had CABG (3%). MI occurred in 17 patients (3%). Figure 1 summarizes the mortality according to the presence of ischemia and previous MI. Most events occurred in patients with ischemia and previous MI, with an annualized event rate of 4.7% compared with 1.9% in the group with a normal stress test and no previous MI ($P=0.004$).

Clinical Predictors of Outcome
By univariable analysis, the clinical predictors of death were age, diabetes mellitus, hypertension, and previous MI; all but hypertension ($P=0.1$) were independently predictive in the multivariable model. Additional nonsignificant clinical variables in the univariable analysis included gender ($P=0.56$), smoking ($P=0.89$), hypercholesterolemia ($P=0.46$), angina ($P=0.62$), and congestive heart failure ($P=0.2$).

Deformation and Predictors of Mortality
The optimal cut point was approximated on the basis of receiver-operating characteristics curves, and this and adjacent values were then entered into a series of multivariate models, together with the same independent clinical predictors listed above. The optimal value was defined as the parameter that maximized the model $\chi^2$ for prediction of mortality (Figure 2). These were an SR, $>-1.2$ seconds$^{-1}$ and $S_{es} >-3.5\%$ for mean values and an SR, $>-1.2$ seconds$^{-1}$ and $S_{es} >-9\%$ for segmental values. Mean SR, and segmental SR, provided stronger models than WMSI. The identification of low risk with mean quantitative parameters, including mean SR, $>-1.2$ (93%) and mean $S_{es} >-3.5\%$ (92%), was not significantly different from its allocation on the basis of peak WMSI $>1.7$ (90%). However, definition based on $>10$ segments with SR, $>-1.2$ led more patients to be identified as low risk (95%; $P=0.02$ versus WMSI), whereas definition based on $>3$ segments with $S_{es} >-9\%$ led fewer to be identified as low risk (73%; $P<0.001$ versus WMSI).

Ischemia by WM, number of ischemic segments, and peak WMSI were significant univariate predictors of death, as were all of the SRI variables at peak (except mean $S_{es}$) (Table 4). In a combined multivariable model including clinical and echocardiographic variables, the only significant independent predictor of death was segmental SR, at peak, with a hazard ratio of 3.6 ($P<0.001$) (Table 4).

Incremental Value of WM and SRI for Predicting Death
A model using only clinical variables (diabetes mellitus, age, and previous MI) gave an overall $\chi^2$ of 12.7. The addition of WMS at either rest or stress increased the power of this model. The addition of the number of abnormal segments based on SR, or $S_{es}$ and mean SR, further increased the prediction from the combination of clinical and stress WM data (Figure 3), although the addition of mean $S_{es}$ was not significant ($P=0.3$).
Figure 2. Model $\chi^2$ values for a series of Cox models using different cutoff values for the WM, average $SR_b$ (systolic strain rate) and $S_{es}$ (end-systolic strain), and number of segments above a threshold level of $SR_b$ and $S_{es}$.
The incremental value of SR appears to be independent of whether WMS demonstrated scar or ischemia. In patients with abnormal WM at rest, mean peak SRs added incremental value to both rest and peak WMSI, increasing \( P < 0.02 \) from 4.2 to 10.0 at rest and from 4.4 to 9.5 at peak \( P < 0.02 \).

The present study demonstrates for the first time that the use of SRI provides additional information to WM analysis alone. Specifically, SRs was found to be an independent predictor of all-cause mortality in patients with known or suspected CAD, incremental to other variables.

### Current Status of SRI

SRI derived from high-frame-rate tissue Doppler data has been studied intensely over the last decade. Although the technique is limited by a number of technical challenges,\(^14\) it has been well validated as a means of accurate measurement of myocardial deformation\(^15,16\) and has been shown to quantify regional function in infarct populations and to demonstrate recovery of stunned myocardium.\(^17,18\) The incorporation of SRI into DSE has been most effective in measuring the low-dose response, where it has been effective in the detection of viable myocardium.\(^19–22\)

However, the use of SRI during peak-dose DSE is difficult because of signal noise, with only 1 published report suggesting incremental benefit.\(^5\) The use of both tissue Doppler and speckle techniques to track the myocardial wall and to perform an automated measurement of SRs appears to increase the sensitivity of DSE compared with expert conventional manual reading.\(^8\) Clearly, although the validation of the technique for identifying anatomic evidence of CAD is important, evidence that the findings are predictive of outcome would help to define the value of the technique. To date, however, no reports of the prognostic value of SRI have been published.

### Prognostic Value of DSE

The clinical markers of outcome in patients with CAD are well defined.\(^23\) Resting left ventricular function is well known to be of incremental value in predicting outcome.\(^24,25\) Although the risk of patients undergoing DSE exceeds that of those who are able to exercise, reflecting the association of events with reduced exercise capacity,\(^26\) a normal DSE carries a good prognosis, with an annualized event rate for cardiac death or infarction of 1.3% and all-cause mortality of 1.8%\(^25\), similar to the all-cause mortality rate of 1.9% per year in the present study. Earlier studies have shown that abnormal WM analysis at both rest and stress are independently predictive of cardiac and all-cause mortality.\(^1,2,24,27–30\) Our findings support this previous experience, showing resting WM abnormality
and ischemia at peak stress to add value to the usual predictors of outcome.

However, even though conventional DSE is predictive of mortality, there are 2 important problems. First, it remains a subjective tool; its accuracy depends on the skills of the user.3 Second, although the extent and severity of abnormality at peak stress are predictive of outcome,31 WM abnormality is known to be relatively poor for distinguishing the true extent of CAD. Indeed, previous work has documented the incremental information obtained by averaging peak systolic velocity in patients with abnormal DSE.32 However, tissue velocity imaging has important limitations in the assessment of regional function, and the present study has shown that SR provides a solution not only to the problem of subjectivity but also to the need to quantify the extent of ischemic and infarcted tissue. Importantly, strain was inferior to peak SR, supporting the findings of diagnostic studies.5,8,33

Prognostic Value of Global Versus Regional Function

Previous studies have shown that peak WMSI response to DSE is one of the strongest independent predictors of adverse cardiac outcomes, adding incremental prognostic information to both clinical data and resting left ventricular function.34 However, the incremental information provided by SR, to WMSI suggests that SRI provides an additional window to cardiac function. First, the use of SRI overcomes potential misinterpretations of WM analysis. For example, SR, may be less load sensitive than standard parameters such as ejection fraction or regional function. Second, SR, may provide information that WM cannot. In this respect, it is of interest that although the mean peak SR, for all segments and the use of peak SR, to categorize segments as normal and abnormal were both predictors of outcome, the segmental value of SR, was the only independent predictor of mortality. Mean SR, was a better predictor for patients with abnormal WM at rest.

Study Limitations

The present prognostic study was set up in 1998, when tissue Doppler acquisitions were less sophisticated and informative than they are now. The frame rates for both tissue Doppler and B-mode images were low in some patients, and only 1 cine loop was stored. Nonetheless, only 5 patients were excluded because of bad image quality.

We followed up patients for all-cause mortality in the belief that the definition of cardiac mortality is unreliable.34 Although it is possible that the predictors of cardiac mortality are different, the main cause of death in this elderly group can be expected to be cardiac, and we would expect the association of cardiac function with cardiac events to be even stronger.

Coronary angiography or myocardial perfusion scintigraphy was not performed in most patients. An alternative design strategy would have been to study patients with defined coronary anatomy, thus linking the predictive capacity of WMS or SR, to anatomic evidence of CAD. However, this approach would not provide information relevant to normal patterns of patient selection.

Unfortunately, changes in medical therapy in the course of follow-up were not tracked in the present study. Although this lack of information is unfortunate, it is unlikely to have influenced the relative prognostic importance of deformation imaging and WM assessment.

Finally, the current measurement of SR, is time consuming. Nonetheless, the adoption of an automated quantitative technique may overcome these limitations.

Conclusions

In patients with known or suspected CAD, mortality can be predicted by the SRI response to DSE. Segmental analysis by SR, at peak appears to be the optimal approach that provides incremental value to WM analysis.

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Disclosures

Professor Marwick received research grant funding from General Electric Medical Systems that is unrelated to this work. The other authors report no conflicts.

References

In contrast, echocardiography and other imaging modalities have provided the ability to measure radial motion of the myocardium on a regional or global basis. The development of strain and strain rate technology has provided the ability not only to assess but also to quantify longitudinal motion (ie, ventricular shortening). Although these measurements have been validated against other methods and shown to be at least comparable to wall motion assessment, their incremental value has until now been unclear. In the present study of 646 patients undergoing dobutamine stress echocardiography for known or suspected coronary artery disease, an automated method was used to measure peak systolic strain rate and end-systolic strain, and results were validated against other methods and shown to be at least comparable to wall-motion assessment. The incremental value of strain rate analysis as an adjunct to wall-motion scoring for assessment of myocardial viability by dobutamine echocardiography has been validated against other methods and shown to be at least comparable to wall-motion assessment. A tool to assess myocardial viability and reperfusion.

**CLINICAL PERSPECTIVE**

Traditionally, echocardiography and other imaging modalities have provided the ability to measure radial motion of the myocardium on a regional or global basis. The development of strain and strain rate technology has provided the ability not only to assess but also to quantify longitudinal motion (ie, ventricular shortening). Although these measurements have been validated against other methods and shown to be at least comparable to wall-motion assessment, their incremental value has until now been unclear. In the present study of 646 patients undergoing dobutamine stress echocardiography for the evaluation of known or suspected coronary artery disease and followed up for all-cause mortality over 7 years, we sought to find out whether strain rate imaging was incremental to conventional wall-motion scoring, which is itself a predictor of outcome. An automated method was used to measure peak systolic strain rate and end-systolic strain, and results were expressed as the number of abnormal segments and the mean systolic strain rate and end-systolic strain per patient. Segmental systolic strain rate was independently predictive of mortality, and this information was incremental to clinical, stress, and wall-motion score data. The findings confirm that the evaluation of longitudinal myocardial motion using strain rate imaging is feasible and that it adds incremental information to the conventional assessment of radial function.


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