Background—Interpretation of dobutamine stress echocardiography (DSE) is subjective and strongly dependent on the skills of the reader. Strain-rate imaging (SRI) by tissue Doppler may objectively analyze regional myocardial function. This study investigated SRI markers of stress-induced ischemia and analyzed their applicability in a clinical setting.

Methods and Results—DSE was performed in 44 patients with known or suspected coronary artery disease. Simultaneous perfusion scintigraphy served as a “gold standard” to define regional ischemia. All patients underwent coronary angiography. Segmental strain and strain rate were analyzed at all stress levels by measuring amplitude and timing of deformation and visual curved M-mode analysis. Results were compared with conventional stress echo reading. In nonischemic segments, peak systolic strain rate increased significantly with dobutamine stress (−1.6±0.6 s⁻¹ versus −3.4±1.4 s⁻¹, P<0.01), whereas strain during ejection time changed only minimally (−17±6% versus −16±9%, P<0.05). During DSE, 47 myocardial segments in 19 patients developed scintigraphy-proven ischemia. Strain-rate increase (−1.6±0.8 s⁻¹ versus −2.0±1.1 s⁻¹, P<0.05) and strain (−16±7% versus −10±8%, P<0.05) were significantly reduced (both P<0.01 compared with nonischemic). Post systolic shortening (PSS) was found in all ischemic segments. The ratio of PSS to maximal segmental deformation was the best quantitative parameter to identify stress-induced ischemia. Compared with conventional readings, SRI curved M-mode assessment improved sensitivity/ specificity from 81%/82% to 86%/90%.

Conclusions—During DSE, SRI quantitatively and qualitatively differentiates ischemic and nonischemic regional myocardial response to dobutamine stress. The ratio of PSS to maximal strain may be used as an objective marker of ischemia during DSE. (Circulation. 2003;107:2120-2126.)

Key Words: stress ischemia echocardiography coronary disease scintigraphy

Dobutamine stress echocardiography (DSE) is well established for detecting inducible ischemia. Ischemia is defined by a regional reduction or deterioration of myocardial thickening or inward motion of the endocardial border.¹⁻³ Reading DSE is subjective and strongly dependent on experience, making more objective markers desirable.⁴⁻⁶ In animal and human studies, myocardial ischemia also caused a delayed onset and termination of systolic shortening.⁷⁻¹⁰ However, it is difficult to visually assess this potential sign of ischemia during DSE.¹¹

Echocardiographic strain-rate imaging (SRI)¹² reliably measures regional myocardial deformation (strain, ε) and deformation rate (strain rate, SR) compared with sonomicrometry.¹¹ Left ventricular wall motion is depicted accurately at rest and during acute and chronic ischemia,¹⁴⁻¹⁶ including dobutamine-induced ischemia in animal models.¹⁷⁻¹⁹ Recent reports on the use of SRI during DSE for viability and ischemia are promising.²⁰⁻²¹

Thus, this study investigates regional myocardial strain rate and strain response during DSE in patients and compares the results with conventional DSE reading, perfusion scintigraphy, and coronary angiography.

Methods

Study Population

The study population (Table 1) comprised 44 consecutive patients referred for DSE to detect the presence or absence of inducible ischemia. Fifteen patients had moderate regional wall-motion abnormalities at rest because of previous infarction. Medication was not discontinued. Patients not in sinus rhythm, with bundle-branch block...
TABLE 1. Characteristics of Patients With and Without Ischemic Response During Dobutamine Stress

<table>
<thead>
<tr>
<th></th>
<th>Nonischemic</th>
<th>Ischemic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25 (57)</td>
<td>19 (43)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62±10</td>
<td>63±9</td>
<td>NS</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>18 (72)</td>
<td>13 (68)</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrate</td>
<td>3 (12)</td>
<td>8 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (76)</td>
<td>15 (79)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (28)</td>
<td>7 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (32)</td>
<td>9 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>64±6</td>
<td>61±4</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline WMA</td>
<td>6 (14)</td>
<td>9 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic segments</td>
<td>0</td>
<td>47 (7.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic segments/patient</td>
<td>0</td>
<td>2.5±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline BP, mm Hg</td>
<td>132/77</td>
<td>134/73</td>
<td>NS/NS</td>
</tr>
<tr>
<td>Peak stress BP, mm Hg</td>
<td>146/79</td>
<td>158/73</td>
<td>NS/NS</td>
</tr>
</tbody>
</table>

Values are n (%) or mean±SD. WMA indicates wall motion abnormalities; BP, blood pressure.

or more than mild valvular heart disease, were excluded. All participants gave written informed consent before the examinations.

**Dobutamine Challenge**

Patients underwent a standard DSE protocol with incremental dobutamine infusion rates of 10, 20, 30, and 40 µg·kg⁻¹·min⁻¹ for 3 minutes each and up to 2 mg of atropine if necessary. Criteria for terminating the test were achievement of target heart rate of (220–age)/0.85 bpm, development of or deterioration of wall-motion abnormalities, angina, ischemic ECG changes, systolic blood pressure increase to >240 mm Hg or decrease to <100 mm Hg, and severe ventricular or supraventricular arrhythmias.

**Echocardiographic Image Acquisition**

Patients were scanned in the left supine position from an apical window with a Vivid Five ultrasound scanner (GE Vingmed). At baseline, at each step of the DSE, and during recovery, 3 heart cycles of the apical 4-, 3-, and 2-chamber views were captured in conventional 2D and color tissue Doppler mode. The image sector was set as narrow as possible, which resulted in a color tissue Doppler frame rate between 133 and 147 frames per second (temporal resolution, 7.5 to 6.8 ms). Echo data were stored digitally for subsequent offline analysis.

**Tissue Doppler Data Processing**

A detailed description of the data processing and its theoretical background is provided by Heimdal et al and Voigt et al. We used dedicated research software (TVI 6.0, GE Vingmed, and TVA, IU. Voigt, University of Erlangen, Germany). Longitudinal strain and strain rate were calculated from color tissue Doppler velocity data (calculation distance, 8 mm). Color-coded strain-rate curve M-modes were reconstructed from each myocardial wall (septal, anteroseptal, anterior, lateral, posterior, and inferior). Wall motion was tracked manually to maintain midwall position. Strain and strain-rate curves were obtained from the middle of the basal, mid, and apical segments of each wall. Thus, an 18-segment model of the left ventricle was used for all further analysis. Three heart cycles were averaged temporally to improve signal-to-noise ratio of the curves. Strain curves were baseline-corrected. Timing of aortic and mitral valve opening (AVO, MVO) and closure (AVC, MVC) was derived from the echo recordings.

**Measurements**

We measured peak systolic strain rate (SRpeak, max), the maximum length change during the entire heart cycle (εmax), strain during ejection time (εe), and postsystolic strain (εps), defined as the maximum length change between AVC and the regional onset of myocardial lengthening caused by early mitral filling (Figure 1). Values are expressed in seconds (strain rate) and percent (strain) and are negative in shortening and positive in lengthening myocardium. To account for systolic shortening and overall curve amplitude, the ratios εps/εpeak and εe/εmax were calculated.

The beginning of myocardial shortening (tmax) and timing of peak systolic strain rate (tmax) were measured relative to AVO and the end of shortening (tmin) relative to AVC. Values are given in milliseconds and as percentage of ejection time.

**Visual Assessment**

Conventional 2D recordings were read by an experienced reader blinded to all patient data using a quad screen with synchronized display of baseline, low-dose, peak, and recovery stage. Ischemia was defined as regional reduction or deterioration of radial myocardial thickening in ≥1 segment. Subsequently, curved M-modes of longitudinal strain rate were assessed visually. Delayed onset of systolic shortening of >20 to 23 ms (3 frames) after AVC, visible deterioration of systolic shortening, and development of postsystolic shortening (PSS) were considered an ischemic response. Artifacts were identified by their band-like shape (Figure 2).

**Scintigraphic Image Acquisition and Data Processing**

During DSE, the radioactive tracer (99mTc-tracer, Cardiolite, Bristol-Meyers-Squibb) was injected at peak stress, and dobutamine was continued for 2 minutes. Scintigraphic images were acquired within 1 hour. Baseline perfusion scintigraphy was performed before the stress test or the day after. Single-photon emission computed tomography (SPECT) was performed with a Multi-SPECT 3 scanner (Siemens) with a low-energy, high-resolution collimator and a gated acquisition protocol. SPECT data were reconstructed with filtered backprojection and visualized with 20% background correction. Corrected tracer uptake at baseline and at peak stress was quantified and compared (ECT-Tool Box, Siemens). As in echocardiography, 18 myocardial segments were defined and assigned as nonischemic, ischemic, or scarred by an experienced reader blinded to DSE results and other patient data.

**Coronary Angiography**

Coronary angiograms were obtained within 4±21 days from the stress echo study, and stenosed vessels were quantified (QCA Quantcor, Siemens). A diameter stenosis of >50% was considered inductive of stress ischemia. To account for variable coronary anatomy, a blinded reader experienced in both coronary angiography and echocardiography assigned myocardial segments to the presumed perfusion territories of stenosed vessels, considering the left coronary to generally supply anterior, anteroseptal, and mid and apical septal segments, the circumflex to supply the lateral wall, and the right coronary artery the basal septal and basal and mid inferior segments. The remaining segments were assigned depending on the relative size of the 3 coronaries and their branches.

**Statistics**

In this study, scintigraphy was the “gold standard” for defining ischemia. Segments with scintigraphic evidence of scar or echocardiographic wall-motion abnormalities at baseline were excluded from the analysis.

If not stated otherwise, all data analysis and comparisons between imaging modalities were performed on a segmental level. Continuous parameters are expressed as mean±SD. Grouped data were tested for normal (gaussian) distribution and equality of SD (Bartlett, Kolmogorov, and Smirnov) and compared by use of a 2-tailed t test. For >2 groups, ANOVA was used. Probability values of P<0.05 were considered statistically significant. Receiver operating characteristics (ROCs) were analyzed for SRI and timing parameters. k statistics were used to compare 2D echo and strain-rate readings with scintigraphy. Sensitivities and specificities were calculated for 2D echo readings and SRI parameters.
Results
No adverse events occurred during DSE. DSE was terminated because of signs of ischemia in 10 patients and after achieving target heart rate in 34 patients. In total, 792 myocardial segments on 4 stress levels each were analyzable (3786 segments). Eighty segments (10.1%) were excluded because of scintigraphic evidence of scar, echocardiographic wall-motion abnormalities, or abnormal strain-rate patterns at rest. On scintigraphy, 19 of 44 patients (43%) had an ischemic response in 47 of 712 segments (7.3%). All patients with inducible ischemia on scintigraphy had significant stenosis (mean, 80 ± 18%) in the supplying coronary artery. No patient without scintigraphic ischemia had significant coronary stenosis. Patients with and without ischemic response did not differ significantly with respect to age, medication, risk factors, baseline ejection fraction, or average blood pressure and heart rate at baseline and peak stress (Table 1).

Feasibility
Conventional visual wall-motion assessment was possible in 97% of the segments. Quantitative analysis of strain and strain-rate curves was possible in only 85% of the segments because of noise and artifacts. Qualitative visual assessment of curved M-modes, however, was achieved in 95% of the segments. As reported previously, interobserver and intraobserver variability of strain and strain-rate measurements ranged from 5% to 10% in our laboratory. The variability of time-interval measurements ranged from 10 to 15 ms.

Quantitative DSE Analysis
Amplitude of Strain and Strain Rate
Data are exemplified in Figures 1 and 2 and summarized in Figures 3 and 4 and Table 2. Baseline parameters of ischemic and nonischemic segments did not differ significantly. During DSE, SRpeak sys clearly increased in nonischemic segments. In contrast to the slight changes in the averaged data (Figure 3b), individual εmax and εps showed a biphasic response in most nonischemic segments. In ischemic segments at peak stress, εps and increase in SRpeak sys were clearly reduced, whereas εmax remained almost constant.

Figure 1. Examples of ischemic and nonischemic stress response. Left, baseline; right, peak stress. Dotted vertical lines indicate MVC, AVO, AVC, and MVC. a, Two-chamber views with color-coded strain-rate overlay and perfusion scintigraphy images in matching orientation. Stress-induced inferoapical ischemia (red arrow). Markers “apical” and “basal” indicate origin of curves below. b, Strain rate. Typical nonischemic patterns at baseline and in basal curve at peak stress. In ischemic apical region, note delayed onset and end of shortening and low peak systolic strain rate at peak stress. Measurements of SRpeak sys, tps, and tps relative to AVO and AVC are illustrated. c, Strain curves. Note early systolic bulging (arrow) and marked PSS in inferoapical curve at peak stress. Other curves show typical nonischemic patterns. Measurements of εmax, εps, and εps are illustrated. Note that in strain curves, position of zero line depends only on definition of “beginning” of cardiac cycle and, thus, is arbitrary. d, ECG, time scale.
Timing of Myocardial Shortening and PSS

Data are provided in Table 2. In all segments at baseline, segmental systolic shortening began at approximately AVO. SRpeak sys occurred in the first third of ejection time. In most segments, shortening at baseline was systolic only; in two fifths, however, PSS of minor amplitude was found. PSS amplitude did not correlate with blood pressure. At peak stress, nonischemic segments showed a similar pattern. The ischemic response at peak stress differed significantly: Onset and peak of shortening were delayed, and all segments showed a markedly delayed end of shortening. This ischemia-induced PSS had a significantly higher amplitude than in nonischemic segments.

By ROC analysis, $\varepsilon_p/\varepsilon_{\text{max}}$ was the best parameter to identify ischemia (area under the curve, 0.899; $P<0.05$). An $\varepsilon_p/\varepsilon_{\text{max}}$ cutoff of 35% identified patients with ischemia with a sensitivity of 82% and a specificity of 85%. $\varepsilon_p/\varepsilon_{\text{max}}$ performed comparably (area under the curve, 0.898; cutoff, 55%; sensitivity, 82%; specificity, 82%). All other SRI parameters had significantly less discriminating power (see Figure 5).

Qualitative DSE Analysis

Conventional 2D Reading

Compared with the scintigraphic gold standard, 78% of the readable ischemic segments were detected by conventional reading. With this, DSE sensitivity and specificity per patient were 81% and 82%, respectively ($\kappa$, 0.62).

Strain-Rate Curved M-Mode Reading

In nonischemic segments, baseline and peak stress curved M-mode patterns differed only in hues and the duration of time intervals. The general sequence of lengthening and shortening events remained unchanged. In stress-induced ischemia, reduction of systolic strain rate (color change) and changes in timing of events (particularly occurrence of PSS) were clearly visible. Of the ischemic segments, 89% were identified, resulting in a DSE test sensitivity and specificity of 86% and 90%, respectively ($\kappa$, 0.74) (Figures 2 and 6).

Discussion

Normal Stress Response of Strain and Strain Rate

In normally perfused myocardium, $\text{SR}_{\text{peak sys}}$ clearly increased with increasing dobutamine dosage (Figure 3a). This is
agreement with previous studies. In contrast, averaged $\varepsilon_{\text{max}}$ and $\varepsilon_t$ changed only little (see Figure 3b), although clear biphasic responses were observed in individual patients. The latter is concordant with reports on animal experiments and comparable to human studies.

**Strain and Strain-Rate Amplitude in Stress-Induced Ischemia**

New or worsening abnormalities of radial wall thickening are the classic echocardiographic signs of ischemia in DSE. Although SRI measures longitudinal deformation, in our study, both $\varepsilon_t$ and the increase in $\varepsilon_{\text{max}}$ were significantly reduced in ischemic segments, confirming earlier studies. Interestingly, $\varepsilon_{\text{max}}$ of ischemic segments remained almost constant because of the increasing or newly occurring PSS.

**Timing of Regional Deformation and PSS**

Only in ischemia, $t_{\text{bos}}$ and $t_{\text{eos}}$ increased significantly because of delayed contraction and marked PSS (Figure 1). Both have been known for years to be markers of myocardial dysfunction. However, the mere presence of PSS, however, is not specific for ischemia, because it is often found at rest in our study in two fifths of all segments at baseline. At peak stress, PSS was found in 100% of the ischemic but also in 47% of the nonischemic segments.

**Criteria for Defining Stress-Induced Ischemia**

Simple amplitude cutoffs for $\varepsilon_t$ or $\varepsilon_{\text{max}}$ during DSE performed rather poorly (Figure 5). Reasons may be both noisy strain-rate signals and differing contractile states of the individuals. Assessing timing by SRI is less sensitive to noise, which may explain the better performance.

### Table 2: Strain Rate Imaging Parameters in Segments With Nonischemic (n=665) and Ischemic (n=47) Response During Dobutamine Stress

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Ischemic</th>
<th>Sign.‡</th>
<th>Baseline</th>
<th>Ischemic</th>
<th>Sign.‡</th>
<th>Sign.§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>70±12</td>
<td>65±11</td>
<td>NS</td>
<td>134±18</td>
<td>130±20</td>
<td>NS</td>
<td>†</td>
</tr>
<tr>
<td>$\text{SR}_{\text{peak sys}}, 1/\text{s}$</td>
<td>-1.6±0.6</td>
<td>-1.6±0.8</td>
<td>NS</td>
<td>-3.4±1.4</td>
<td>-2.0±1.1</td>
<td>†</td>
<td>*</td>
</tr>
<tr>
<td>$\varepsilon_{\text{max}}, %$</td>
<td>-20±6</td>
<td>-19±8</td>
<td>NS</td>
<td>-23±9</td>
<td>-20±10</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>$\varepsilon_t, %$</td>
<td>-17±6</td>
<td>-16±7</td>
<td>NS</td>
<td>-16±9</td>
<td>-10±8</td>
<td>†</td>
<td>*</td>
</tr>
<tr>
<td>$\varepsilon_{\text{ps}}, %$</td>
<td>0.9±3.4</td>
<td>0.9±3.5</td>
<td>NS</td>
<td>0.4±4.1</td>
<td>-6.7±4.5</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>$\varepsilon_t/\varepsilon_{\text{max}}, %$ of $\varepsilon_{\text{max}}$</td>
<td>-4±16</td>
<td>-2±19</td>
<td>NS</td>
<td>-2±17</td>
<td>39±30</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>PSS, % of segment</td>
<td>39</td>
<td>43</td>
<td>47</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{\text{bos}}, %$ of ET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\varepsilon_{\text{max}}$, %</td>
<td>$-2.1±1.4$</td>
<td>$-2.4±1.5$</td>
<td>NS</td>
<td>$-2.6±1.8$</td>
<td>$-6.7±4.5$</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>$\varepsilon_t/\varepsilon_{\text{max}}, %$ of $\varepsilon_{\text{max}}$</td>
<td>10±8</td>
<td>15±14</td>
<td>*</td>
<td>12±14</td>
<td>39±30</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>$t_{\text{bos}}, %$ of ET</td>
<td>9±57 (3±17)</td>
<td>18±45 (6±14)</td>
<td>NS</td>
<td>12±66 (7±40)</td>
<td>47±45 (28±28)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>$t_{\text{eos}}, %$ of ET</td>
<td>31±23</td>
<td>35±25</td>
<td>NS</td>
<td>31±43</td>
<td>55±38</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>$\varepsilon_{\text{ps}}, %$</td>
<td>24±78 (8±26)</td>
<td>32±63 (11±22)</td>
<td>NS</td>
<td>24±77 (15±46)</td>
<td>79±45 (47±28)</td>
<td>†</td>
<td>†</td>
</tr>
</tbody>
</table>

ET indicates ejection time.

*P<0.05, †P<0.01.

‡Significance vs segments with nonischemic stress response.

§Significance vs baseline.

| Segments with PSS only. |
M-mode reading results. To separate “PSS and to increase the specificity of this highly chemic
and reduced systolic shortening.

**Clinical Implications**

DSE is based on the visual assessment of regional myocardial function and thus is subjective. SRI is feasible in the clinical setting, measures longitudinal myocardial deformation directly independently of translation, and offers parameters comparable and possibly superior to the visually assessed regional (radial) wall thickening. PSS is a well-known sign of ischemia. Because of its relatively low amplitude and, in particular, its short-lived nature, however, its visual recogni-
tion (known as “contraction asynchrony”) is difficult.\(^{11}\) SRI allowed us to quantify PSS and, with a cutoff value of \(\varepsilon_p/\varepsilon_{max} > 35\%\), resulted in a sensitivity of 82% and specificity of 85% for the detection of stress-induced ischemia.

A particularly practical approach is the visual comparison of color-coded strain-rate curved M-modes at baseline and during stress, because they combine information on the delayed onset of shortening and deterioration of systolic function (akinesia, yellow to green; dyskinesia, yellow to blue) and are highly sensitive to the occurrence of PSS. Our data suggest that visual interpretation of strain-rate curved M-modes is more accurate than conventional visual DSE assessment (sensitivity, 86% versus 81%; specificity, 89% versus 82%; see Figure 6).

**Limitations**

Strain and strain-rate measurements are subject to noise, angle artifacts, and interindividual variability. Therefore, relative parameters (in particular, \(\varepsilon_p\) relative to \(\varepsilon_{max}\) or \(\varepsilon_d\)) and time intervals should be preferred.

A further limitation of SRI is that currently, unlike visual or magnetic resonance analysis, only apical scanning offers comparable information on all segments, which restricts analysis to longitudinal deformation only. However, the good spatial and unrivaled temporal resolution of SRI make it uniquely suited to assess short-lived regional phenomena like PSS.

In our analysis, we omitted segments with wall-motion abnormalities at rest for the sake of clarity. Further studies will be needed to address SRI characteristics of scar, partial scar, and dysfunctional but viable myocardium during DSE.

Although SRI analysis is currently still time consuming, it is clinically applicable, and with modest software improvements, measurements will be a matter of a few minutes at most, similar to flow Doppler.

**Conclusions**

Doppler SRI is feasible and able to objectively differentiate ischemic and nonischemic myocardium. In particular, the delayed end of myocardial shortening after AVC (PSS) identifies stress-induced ischemia with high sensitivity and if amplitude of PSS (\(\varepsilon_p/\varepsilon_{max}\) or \(\varepsilon_p/\varepsilon_d\)) is considered, good specificity, possibly superior to that of conventional visual DSE assessment.

**Acknowledgments**

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Strain-Rate Imaging During Dobutamine Stress Echocardiography Provides Objective Evidence of Inducible Ischemia

Jens-Uwe Voigt, Bert Exner, Kristin Schmiedehausen, Cord Huchzermeyer, Udo Reulbach, Uwe Nixdorff, Günther Platsch, Torsten Kuwert, Werner G. Daniel and Frank A. Flachskampf

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