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Strain Echocardiography Tracks Dobutamine-Induced Decrease in Regional Myocardial Perfusion in Nonocclusive Coronary Stenosis

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OBJECTIVES This study was designed to determine whether strain echocardiography parameters reflect changes in regional myocardial perfusion during dobutamine stress.

BACKGROUND Strain echocardiography depicts regional myocardial mechanical activity. Ischemia has been shown to reduce systolic strain rate (sSR) and prolong the time to regional lengthening (T_{RL}). In an experimental model, we tested whether sSR and T_{RL} tracked dobutamine-induced changes in regional myocardial perfusion (regional myocardial blood flow [RMBF]), as measured by colored microspheres.

METHODS We used a closed-chest pig model of nonocclusive coronary stenosis (n = 14) created by inflating an angioplasty balloon in the proximal left anterior descending artery. Invasive hemodynamics, RMBF, and strain parameters were measured at baseline and peak dobutamine stimulation before and during the coronary stenosis. We compared segments with reduced RMBF versus those with preserved RMBF at peak dobutamine stimulation.

RESULTS Peak sSR correlated with RMBF (r = 0.70). In the absence of coronary stenosis, dobutamine stimulation caused a significant increase in RMBF and sSR and a decrease in T_{RL}. This response was blunted during coronary stenosis. Using the "best cutoff" method, the sensitivity and specificity for prediction of reduced RMBF (ischemia) was 81% and 91% for sSR and 65% and 91% for T_{RL}, respectively. These changes occurred in the absence of any change in global systolic and diastolic function (dP/dT_{max}, dP/dT_{min}, and tau).

CONCLUSIONS Novel strain parameters that depict regional myocardial mechanics are able to predict changes in RMBF during dobutamine stress. Quantitative strain parameters may complement current echocardiographic techniques for ischemia detection and potentially improve the accuracy and reproducibility of stress echocardiography. (J Am Coll Cardiol 2004;44:1664–71) © 2004 by the American College of Cardiology Foundation

Myocardial ischemia can manifest as an abnormality in regional contractile activity (altered systolic wall motion) or regional relaxation (asynchrony and/or delay in onset of relaxation) (1–3). Strain echocardiography (SE) measures the rate (strain rate) and extent (strain) of regional myocardial shortening and lengthening (4–7). Because it is less influenced by translational motion and tethering, SE may be superior to tissue Doppler imaging in evaluating changes in regional myocardial activity (8).

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Regional ischemia is associated with reduced systolic strain rates (sSR) and prolongation of the time to onset of regional lengthening (T_{RL}) (7,9). Similarly, stress-induced change in sSR or T_{RL} is blunted in ischemic compared with nonischemic segments (3). Doppler-derived parameters (sSR) are influenced by the angle of insonation, whereas temporal parameters (T_{RL}) are relatively independent of this angle. The lack of imaging techniques with adequate temporal resolution has hitherto limited the clinical application of temporal parameters in the detection of ischemia. Because of its high temporal and spatial resolution, SE may facilitate the application of novel quantitative parameters in ischemia detection. High-resolution tracking of regional myocardial activity by SE may provide a valuable and quantifiable means of detecting inducible ischemia with implications for stress echocardiography. Voigt et al. (10) recently demonstrated the feasibility and accuracy of strain rate amplitude and timing parameters in predicting ischemia during clinical dobutamine stress echocardiography.

In a closed-chest pig model of nonocclusive coronary stenosis, we tested whether sSR and T_{RL} tracked dobutamine-induced changes in regional myocardial perfusion, as measured by colored microspheres.

METHODS

Animal model (Fig. 1). This protocol was approved by the Institutional Animal Care and Use Committee and conformed to the position of the American Heart Association on research animal use. Female pigs (n = 23) weighing 40 to 50 kg were sedated with ketamine (20 mg/kg) and xylazine (2 mg/kg) intramuscularly. After intubation and

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Abbreviations and Acronyms

LAD = left anterior descending artery
LV = left ventricle/ventricular
RMBF = regional myocardial blood flow
SE = strain echocardiography
sSR = systolic strain rate
T_{RL} = time to regional lengthening

connection to a mechanical ventilator, anaesthesia was maintained with 1.5% inhaled isoflurane. A heating pad was used to maintain body temperature. Cutdown and soft dissection were used to expose blood vessels on both sides of the neck. The carotid arteries were canulated with 9F sheaths for hemodynamic monitoring (left carotid artery) and introduction of a guide catheter and coronary angioplasty balloon catheter (right carotid artery). Both internal jugular veins were canulated with 7-F sheaths for drug and intravenous fluid administration. Both femoral arteries were cannulated by the Seldinger technique, with one 8-F sheath for left ventricular (LV) pressure recording using a 7-F open-end micromanometer-tipped pigtail catheter (Millar Instruments, Houston, Texas), and the other for withdrawal of arterial blood samples. All animals received heparin during the procedure to maintain an activated clotting time >300 s. Hemodynamics and electrocardiograms were monitored continuously and blood samples were drawn half-hourly for electrolytes and arterial blood gases.

Under fluoroscopy guidance, a 7-F guide catheter was advanced over a guide wire through the right carotid artery sheath to engage the left coronary artery, using standard angiography techniques with intermittent contrast dye injections. An angioplasty balloon catheter was advanced through the guide catheter to a position just distal to the takeoff of the first diagonal branch. The balloon was then inflated to cause a moderate stenosis in the mid-portion of the left anterior descending artery (LAD). Severity of occlusion was visually assessed by injecting contrast dye selectively into the LAD and using the Thrombolysis In Myocardial Infarction flow grading system with the aim of achieving Thrombolysis In Myocardial Infarction flow grade 1 or 2. Using this method in our pilot experiments, we successfully created stenoses that consistently reduced dobutamine-induced increase in regional blood flow by ~50% of the prestenosis level.

Invasive hemodynamic assessment. Micromanometer-tip high-fidelity catheters (Millar Instruments) were placed via the carotid and femoral arteries to monitor proximal ascending aortic pressure and LV pressure, respectively. Analog signals from electrocardiography, aortic, and LV pressures were digitized online. Heart rate, aortic, and LV pressure tracings were analyzed offline using custom analysis software (Windaq Software; Dataq Instruments, Akron, Ohio). The pressure crossovers of the aorta and LV indicate aortic valve opening and closure. The time constant of isovolumic relaxation (tau) and first-time derivative of maximal positive and negative LV pressure (dP/dT_{max} and dP/dT_{min}) were calculated from the LV pressure data. A modified Weiss semilogarithmic zero-asymptote model was used to calculate tau using data from the isovolumic relaxation phase starting at peak dP/dT_{min} and ending 5 mm Hg above LV end-diastolic pressure (11). Tau calculations using this

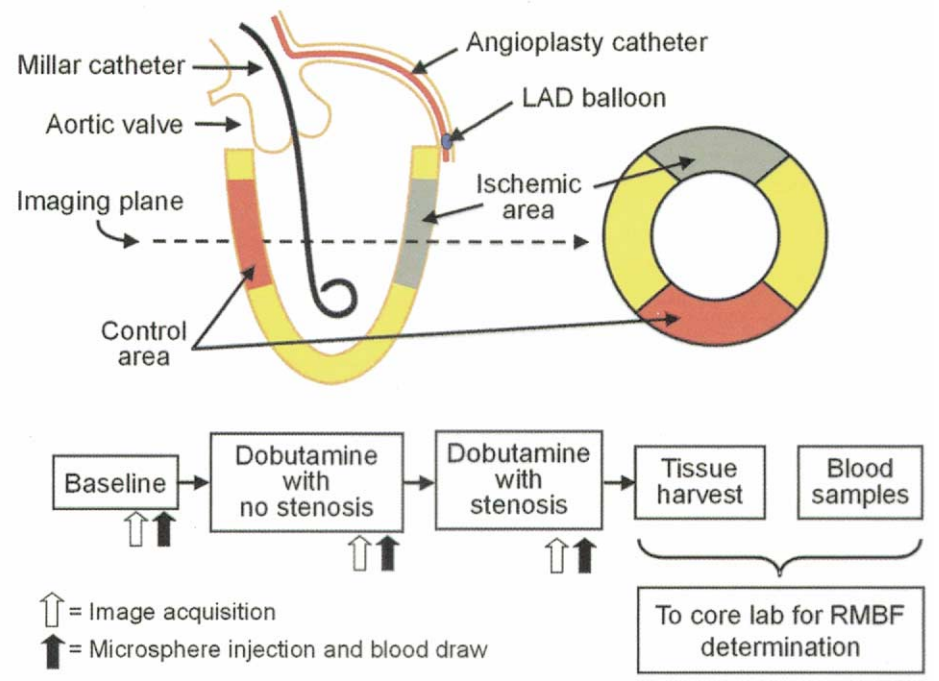

Figure 1. Schematic representation of the animal model and study flow (see text for details). LAD = left anterior descending artery; RMBF = regional myocardial blood flow.

model have been shown to have less beat-to-beat variability than the nonzero asymptote models and may be beneficial during myocardial ischemia (12).

Measurement of regional myocardial blood flow. Regional myocardial blood flow (RMBF) was measured using 15-μm diameter BioPAL microspheres (BioPAL; BioPhysics Assay Laboratory Inc., Worcester, Massachusetts) labeled with stable (nonradioactive) isotopes and used in a similar fashion as radioactive microspheres (13).

Microspheres were injected into the LV via the pigtail catheter at rest and peak dobutamine (before and during balloon inflation). Microsphere dose was determined by the animal weight (dose = $1.2 \times 10^6 + [1.9 \times 10^5]$[mass of animal in kg]). A reference blood sample was withdrawn from the femoral artery at a fixed rate of 4.0 ml/min for 2 min. At the end of the experiment, the animal was euthanized with 100 mg/kg intravenous pentobarbital, the chest was opened via median sternotomy, and the position of the balloon in the LAD was marked with a silk suture. The heart was extracted and dissected to yield a 1-cm-thick mid-ventricular cross-section slice. This slice was sectioned into six sectors corresponding to the mid-ventricular short-axis echocardiographic segments. Tissue sections were weighed and placed in tracer-free polypropylene vials. Tissue samples from the anterior and anteroseptal segments (ischemic) and inferior and inferolateral segments (control) together with arterial blood samples were sent to the manufacturer's laboratory for measurement of microsphere content and calculation of blood flow.

Dobutamine stress. Graded dobutamine infusion (5, 10, and 20 μg/kg/min for 5 min at each dose) was administered before and during the stenosis. Data were collected at baseline and peak dobutamine stress (2).

Echocardiography. Conventional and tissue Doppler images were acquired at baseline, with the uninflated balloon catheter in situ (without stenosis), and during balloon inflation (stenosis). A 3.5-MHz phased-array transducer with a Vivid 5 Ultrasound machine (GE Medical Systems, Milwaukee, Wisconsin) was used to obtain a parasternal short-axis view of the heart, using a narrow sector angle (30°) and high frame rates (>200 frames/s). In our pilot experiments, we determined that reliable and consistent transthoracic images were available only from the parasternal short-axis view. This view allowed visualization of the anterior, anterior-septum, inferior, and inferolateral segments at the mid-ventricular level. Four cardiac cycles were acquired during normal sinus rhythm, at baseline, and during graded dobutamine infusion, before and during balloon inflation.

Image analysis was performed offline using a custom semiautomated MatLab-based software program developed in our laboratory. For strain rate analysis, a sample region (strain distance 5 mm) was placed in the endocardial portion of each segment to yield peak radial sSR. Peak sSR was the maximum positive value of the systolic strain rate signal. In short-axis imaging, SE evaluates regional myocardial thickening in the radial direction yielding positive strain rate values. A previously described software tool was used for T_{RL} measurements (3). Time to regional lengthening is defined as the time interval from the peak of the R-wave on the electrocardiogram to the transition from regional shortening to lengthening pattern on color M-mode SE in each segment (T_{RL} is corrected for heart rate and expressed in ms).

Mean peak sSR and T_{RL} for each segment were the average of values from three to five cardiac cycles. The changes in peak sSR and T_{RL} between baseline and peak dobutamine were normalized to the baseline values and expressed as percent change.

Ischemia was defined as a 50% decrease in RMBF at peak dobutamine stress compared with prestenosis levels. This criterion was used on the basis of published clinical data that indicate a mean decrease in dobutamine-induced regional blood flow of 50% in regions subtended by coronary arteries with >50% diameter stenosis (14,15). Accordingly, segments subtended by the LAD (anterior and anteroseptal) were excluded if there was <50% decrease in RMBF, and segments in the control vascular territory (inferior and inferoseptal) were excluded if RMBF decreased >30% compared with baseline levels.

Statistical considerations. Continuous variables were expressed as mean values ± SD. Change in sSR and T_{RL} values, without and with coronary stenosis, was analyzed using a paired two-tailed *t* test on the mean values for ischemic and nonischemic segments within each animal. This was done to allow for the non-independence of individual segments within each animal. Receiver operating characteristic curves were plotted for sSR and T_{RL} separately and in combination, using the linear combination suggested by logistic regression modeling. The bootstrap method (resampling animals with replacement) was used to compare the areas under the separate sSR and T_{RL} curves. The incremental value of adding each variable to the model containing the other variable was done using logistic regression with generalized estimating equations using SAS software, version 8 (SAS Institute Inc., Cary, North Carolina), to adjust for within-animal correlation. Incremental value was inferred when the parameter estimate of the variable was significant when adjusting for the other. A p value of <0.05 was considered statistically significant.

RESULTS

Pilot experiments performed on the initial eight animals were used to develop the model and study design. Of the subsequent 15 consecutive experiments, data from one animal were excluded (cardiac arrest and circulatory shock at baseline), leaving 14 for analysis. Segments with poor signal quality and those that did not fulfill RMBF criteria for ischemia and control segments (8 of 56 segments; 14%) were excluded from analysis. There was at least one analyz-

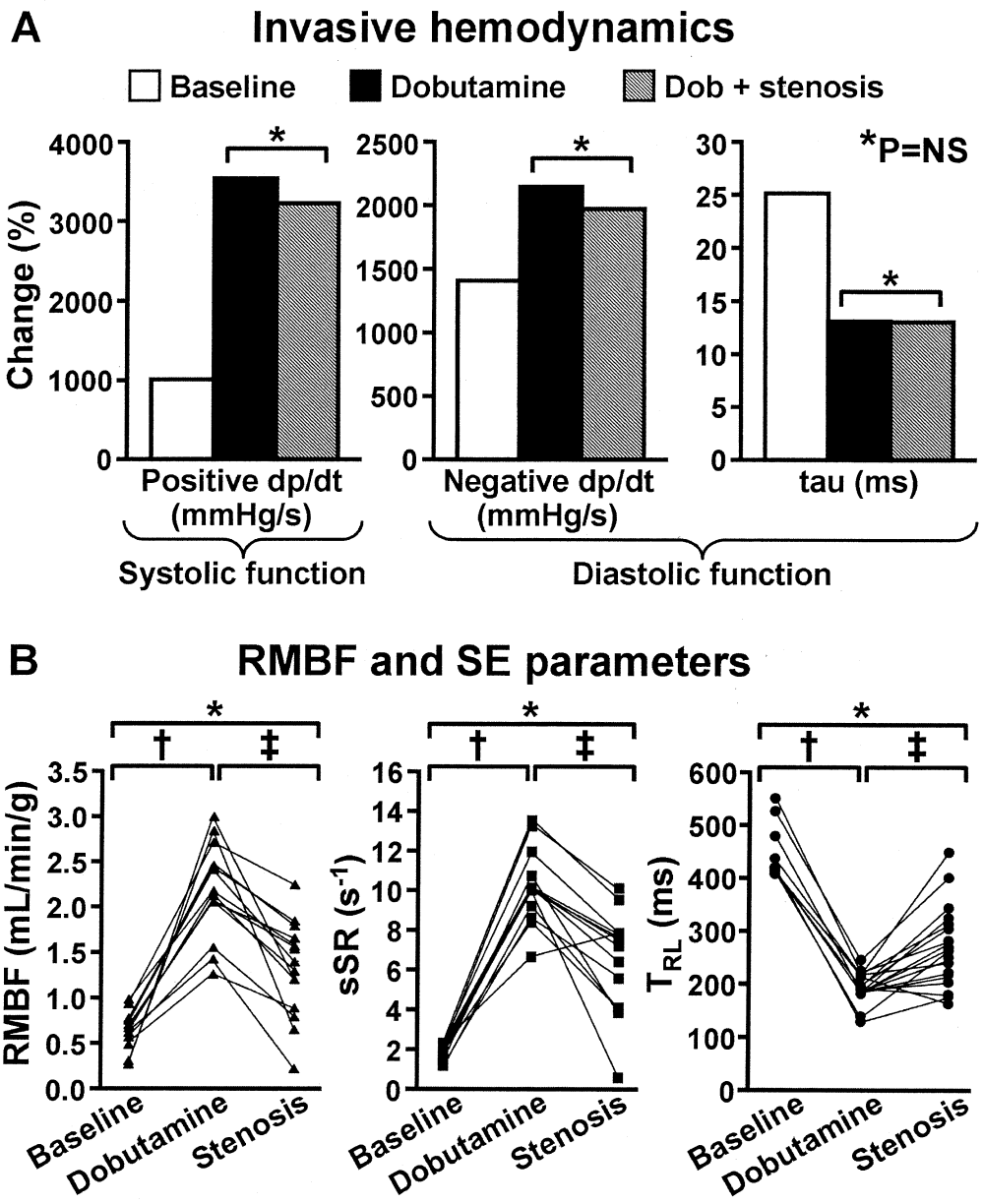

Figure 2. Invasive hemodynamic parameters of global systolic and diastolic function at peak dobutamine (Dob) were similar with and without stenosis **(A)**. Regional myocardial blood flow (RMBF) at peak dobutamine was lower with compared to without stenosis **(B, left panel)**. Peak change in systolic strain rate (sSR) and time to regional lengthening (T_{RL}) at peak dobutamine was significantly blunted with compared to without stenosis **(B, middle and right panels, respectively)**. *$p < 0.01$ between baseline and dobutamine + stenosis; †$p < 0.01$ between baseline and dobutamine; ‡$p < 0.01$ between dobutamine and dobutamine + stenosis. SE = strain echocardiography.

able segment for each study region (ischemic and nonischemic) in all animals.

Hemodynamics. The mean rate pressure product was 9,462 ± 3,015 at baseline, 23,345 ± 3,073 at peak dobutamine without stenosis, and 21,602 ± 3,549 at peak dobutamine with stenosis ($p < 0.001$ for baseline vs. either dobutamine stage, and 0.07 for dobutamine without vs. with stenosis). Compared with baseline, dP/dT_{max} and dP/dT_{min} increased, and tau decreased, with dobutamine stimulation. There were no significant differences in these variables at peak dobutamine, without or with stenosis (p = NS for all) (Fig. 2A).

Regional myocardial blood flow. Mean dobutamine-induced increase in RMBF was significantly higher without compared to with stenosis (430 ± 56% vs. 300 ± 42%, $p < 0.01$) (Fig. 2B).

Strain echocardiography. Peak sSR correlated closely with RMBF ($r = 0.70$) (Fig. 3). Percent change in sSR (355 ± 119% vs. 585 ± 191%, $p < 0.0001$) and T_{RL} (38 ± 14% vs. 55 ± 7%, $p < 0.0001$) from baseline to peak dobutamine stress was significantly lower with compared to without stenosis (Fig. 2B). Representative SE images are presented in Figure 4. The sensitivity and specificity for detection of >50% reduction in peak RMBF for each parameter was

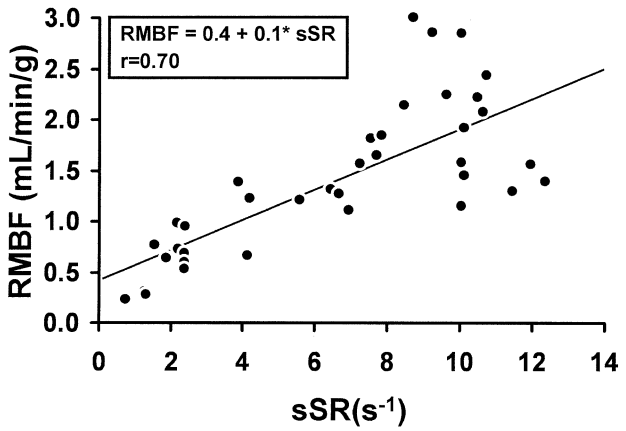

Figure 3. Correlation between peak systolic strain rate (sSR) and regional myocardial blood flow (RMBF).

determined after initially establishing the best cutoff value. The best cutoff value was chosen to minimize the number of misclassifications of events and nonevents. Using the best cutoff, the sum of the number of events that would be classified as nonevents and the number of nonevents that would be classified as events is minimized. By this method, the best cutoff value for sSR was an increase of 412% that yielded a sensitivity and specificity of 81% and 91%, respectively. Similarly, the best cutoff value for T_{RL} was a decrease of 46%, which yielded a sensitivity and specificity of 65% and 91%, respectively (Fig. 5). When both variables were included in the logistic regression model for ischemic segments, sSR ($p = 0.02$) and T_{RL} ($p = 0.002$) were independently predictive of ischemia. Receiver operating characteristic curves plotted for sSR and T_{RL} change revealed an area under the curve of 87% for sSR and 85% for T_{RL}, and these were not significantly different by bootstrap analysis (1,000 bootstrap samples; $p = 0.25$). The logistic regression model in ischemic segments, based on sSR and T_{RL} in combination (area under the curve = 93), demonstrated that compared with sSR alone, a combination of sSR and T_{RL} was more predictive of ischemia ($p = 0.05$). Similarly, when compared with T_{RL} alone, a combination of sSR and T_{RL} was more predictive of ischemia ($p = 0.01$).

DISCUSSION

We demonstrate a close correlation between sSR and RMBF. Our data demonstrate a quantifiable reduction of dobutamine-induced change in peak sSR and T_{RL}, with induced ischemia. Strain echocardiography parameters correlated closely with RMBF. Novel SE-derived indicators of myocardial mechanics (sSR and T_{RL}) appear to reliably predict the reduction in peak RMBF during dobutamine infusion in the presence of a coronary stenosis. Our data

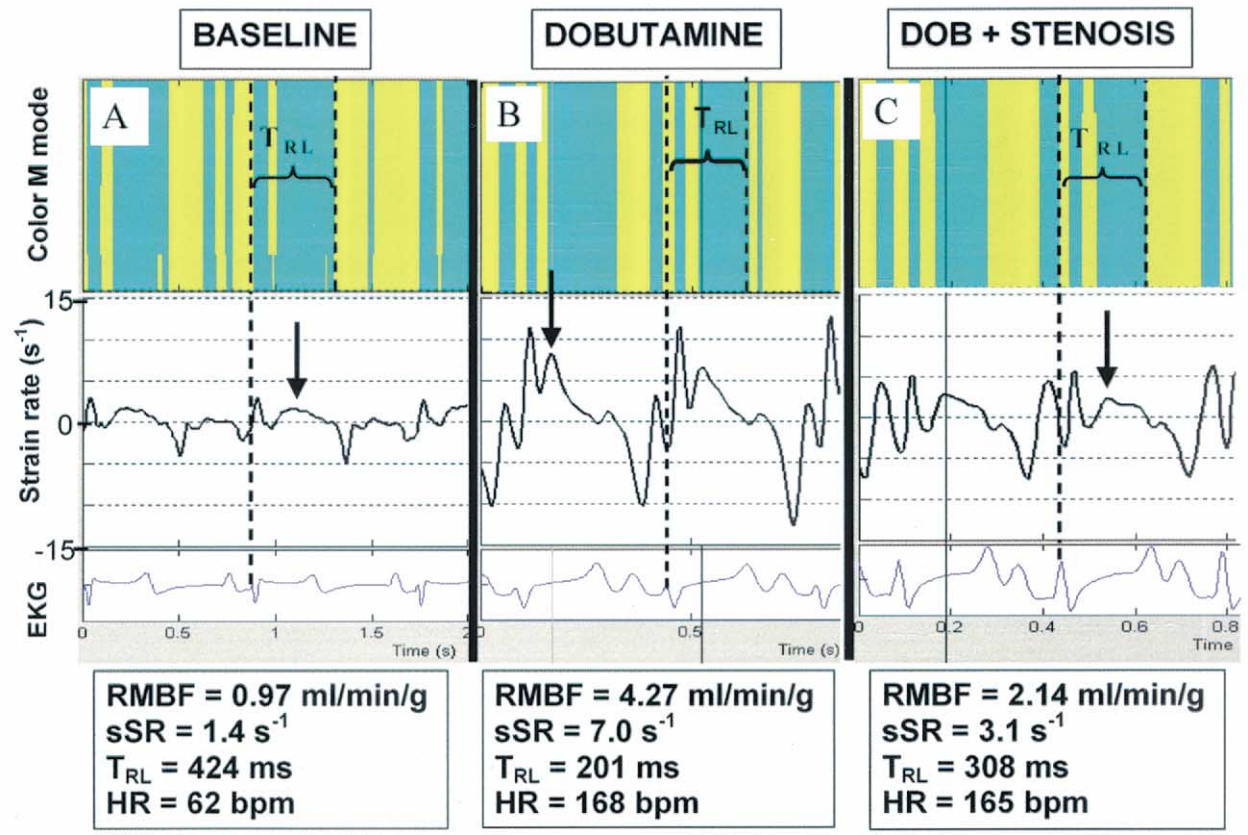

Figure 4. Representative color M-mode and strain rate images at baseline **(A)**, dobutamine without stenosis **(B)**, and dobutamine (DOB) with stenosis **(C)**. Despite similar increases in heart rate (HR), regional myocardial blood flow (RMBF) is reduced, and the dobutamine-induced increase in sSR and a decrease in T_{RL} **(B)** significantly blunted in the presence **(C)** versus absence **(B)** of coronary stenosis. Other abbreviations as in Figure 2.

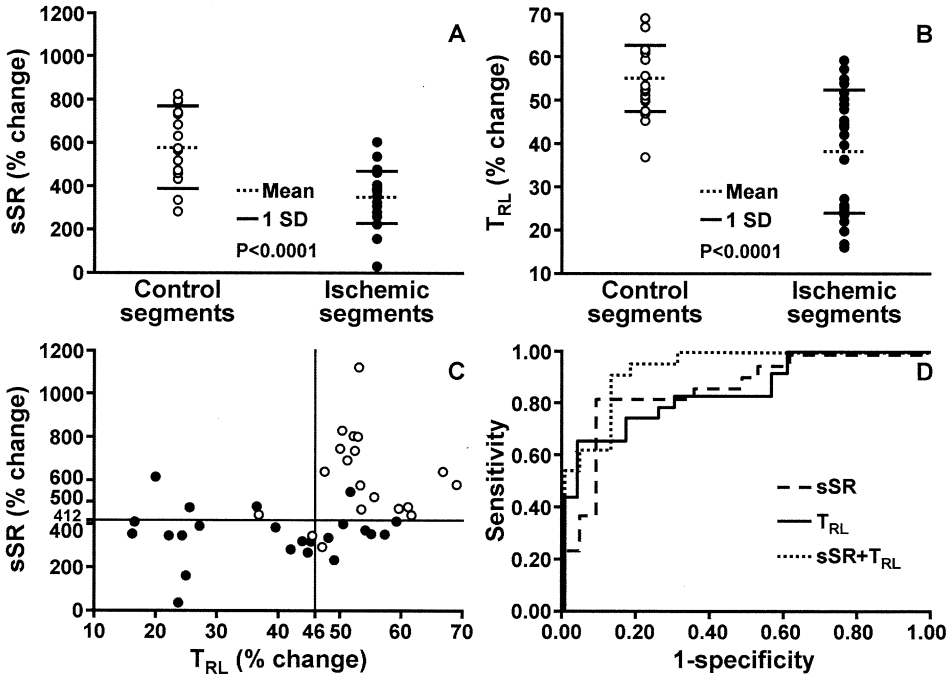

Figure 5. Change in sSR **(A)** and T_{RL} **(B)** from baseline to peak dobutamine stress was significantly lower in ischemic versus normal segments (both $p < 0.0001$; dashed lines = mean, solid lines = 1 SD). Using a combination of the best cutoff values for change in sSR and T_{RL} significantly increased the specificity compared with sSR and T_{RL} alone **(C)**. **Open circles** = control segment response; **black circles** = ischemic segment response. **(D)** Receiver operating characteristic curves demonstrated that the area under the curve was similar for sSR compared with T_{RL}, and was higher for sSR + T_{RL} compared with T_{RL} alone ($p = 0.01$) and for sSR alone ($p = 0.05$). Abbreviations as in Figure 2.

show that changes in regional myocardial function occurred in the absence of change in global systolic or diastolic function as indicated by invasive global hemodynamic parameters (dP/dT_{max}, dP/dT_{min}, and tau).

Strain echocardiography is a recently described technique that has been validated using sonomicrometric crystals, gel phantoms, and magnetic resonance imaging. Strain echocardiography accurately depicts regional deformation and is less influenced by myocardial tethering and cardiac translational motion (4–6,16). Techniques with high temporal resolution such as SE can accurately track rates of systolic shortening and phase change (contraction to relaxation and vice versa). The feasibility of SE during stress echocardiography has been recently demonstrated (17,18). Ischemia-induced decrease in systolic thickening rates can be detected by sSR. A decrease in sSR with coronary occlusion and a blunted increase in sSR with stress-induced ischemia have been previously demonstrated. However, this method necessitates accurate determination of peak sSR, which is influenced by image quality and angle of insonation.

In contrast, T_{RL} identifies the time taken by a myocardial segment to change from shortening to lengthening pattern at which time the negative polarity of systolic strain switches to the positive polarity of diastolic strain in the longitudinal plane and positive to negative in the radial (short-axis) plane. The high temporal resolution of SE (~5 to 10 ms) enables accurate delineation of such a phase change and detailed interrogation of regional cardiac mechanical events. Detection of phase change such as regional transition from contraction to relaxation, or vice versa, is less dependent on image quality and angle of insonation. Asynchrony of regional relaxation has been previously demonstrated in animal and clinical studies (19–21). Delayed onset of relaxation in a particular ischemic segment would result in a prolonged T_{RL}. Ischemia-induced cellular energy deficiency, resulting in slower actin-myosin dissociation and slower cytosolic calcium ion removal, may form the pathophysiologic basis for a prolonged T_{RL} with ischemia (22). We have previously shown that T_{RL} is prolonged during coronary occlusion (9). We have also shown that T_{RL} decreases with dobutamine stress are blunted in segments that develop stress-induced wall motion changes (3).

In this study, we hypothesized that sSR and T_{RL} would track changes in regional myocardial perfusion as determined by colored microspheres. To test this hypothesis we attempted to mimic clinical coronary artery disease in an animal model. We used a closed-chest model because pericardiectomy alters regional and global cardiac mechanics and could confound the interpretation of the changes seen with ischemia. Transthoracic ventricular short-axis images were obtained at baseline, at peak dobutamine infusion without stenosis, and at peak dobutamine infusion during stenosis. Regional myocardial perfusion was determined using stable colored microspheres. The microspheres are not radioactive during the experiment, which eliminates the logistic issues related to radioactive microspheres.

Our data show that sSR and T_{RL} closely correlated with RMBF. In the absence of significant coronary stenosis,

previous published data suggest that there is usually a two- to threefold increase in regional perfusion with dobutamine, which is usually reduced in the presence of significant coronary stenosis (14,15,23–25). Our values of RMBF before stenosis were similar, but the dobutamine-induced increase in RMBF was higher than that previously reported in experimental and clinical studies. Potential reasons for disparity in flow in our study compared with the previous studies may be a function of the measurement technique, the size of the myocardial sample used to calculate regional flow, and the rate-pressure product achieved in our study, which was higher than that obtained in most clinical studies. It is also possible that our angioplasty balloon did not maintain a stable high-grade stenosis during the dobutamine stress. The presence of infarcted myocardium and significant endothelial dysfunction in patients may also explain the lower RMBF in clinical studies.

The increase in sSR is greater than the reported increase in wall thickening during dobutamine infusion. The increase in systolic wall thickening of normally perfused myocardium with dobutamine infusion ranged from 30% to 100%. In an experimental study, despite a fivefold increase in RMBF, systolic wall thickening increased by ~100% (26). In clinical studies, normal subjects demonstrated an increase in wall thickening with dobutamine of 70% to 120%, using echocardiography, magnetic resonance, and computed tomography (24,27,28). In contrast, our data demonstrate a five- to six-fold increase in sSR, with a similar increase in RMBF (Fig. 3) and at doses of dobutamine similar to those used in the experimental and clinical studies quoted earlier. These data suggest that SE may provide more sensitive parameters for tracking changes in regional blood flow than conventional echo parameters. These findings support the idea that SE may be more useful than conventional echocardiography for the diagnosis of coronary disease.

Dobutamine infusion normally causes an increase in sSR and a decrease in T_{RL}. Our results show that a blunted sSR and T_{RL} response at peak dobutamine stress accurately detect reductions in RMBF. Although, our data validate the results recently published by Voigt et al. (10), there are some differences that warrant clarification. The strain rates were lower and the area under the curve for sSR prediction of coronary stenosis was lower in the Voigt study. Potential explanations for these discrepant results include the fact that radial, not longitudinal, strain rates were examined in our study; the presence of obstructed coronary arteries in the human study with resting ischemia; possible partial thickness infarct in the ischemic region; and the inability to optimally align the myocardial wall to the ultrasound beam. Nonetheless, clinically relevant cutoff values will need to be established and validated in larger clinical trials.

Dobutamine stress echocardiography is a relatively safe technique, widely used to detect inducible ischemia and aid patient management in a variety of clinical situations (29–32). Ischemia is recognized echocardiographically by reduced rate and extent of systolic shortening (thickening) of the myocardium. However, current interpretation of stress echocardiography is subjective and highly variable (33). Currently, visual estimation of the extent of wall thickening is used to detect ischemia by echocardiography. However, the temporal resolution of the human eye is limited (34). Several attempts have been made to quantify stress echocardiography interpretation but are yet to be incorporated into routine clinical practice.

Both sSR and T_{RL} are quantitative parameters that can help enhance the accuracy and reproducibility of stress echocardiography.

Study limitations. In the closed-chest porcine model transthoracic imaging is usually limited to a mid-ventricular short-axis view. Although long-axis views are possible, the same imaging plane is not always available and images are frequently foreshortened. We therefore restricted our imaging to short-axis views and imaged two anterior segments and two inferior/posterior segments at the mid-ventricular level. This imaging was sufficient for purposes of our study. Our results may not be applicable to other cardiac segments. Although most settings are similar to those used in clinical dobutamine stress echocardiography, the narrow sector is not standard clinical practice and may affect feasibility of clinical SE.

Our study was designed to evaluate sSR and T_{RL} at baseline and peak stress only. We did not perform stagewise analysis. Because tissue velocity is low/absent and noisy in the segment(s) closest to the transducer (anterior segments), we did not compare strain rates with tissue velocity. We did not have adequate power to test whether SE parameters provide incremental information over visual wall-motion analysis. This question would be best addressed in a clinical study. Our sample size is small (48 segments). There is animal-to-animal variability in the RMBF and SE parameters, which may somewhat limit direct application of these results to clinical practice. Because we did not occlude the coronary artery, we did not create a partial or full thickness infarction. Thus we are unable to comment on the potential clinical value of postsystolic thickening, a finding often seen in clinical SE. Lastly, all studied segments were normal at baseline. Thus, we are unable to comment on the efficacy of these SE parameters when segments are hypokinetic/akinetic at baseline.

Conclusions. Novel SE parameters that depict regional myocardial mechanics correlate closely with RMBF and are able to predict changes in RMBF during dobutamine stress. These quantitative parameters may complement current echocardiographic techniques for ischemia detection. Strain echocardiography may improve the sensitivity and reproducibility of stress echocardiography and introduces new paradigms in the detection of inducible ischemia.

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