

**Objectives**

The aim of this study was to assess and validate 2-dimensional (2D) strain for the detection of ischemia during dobutamine stress echocardiography (DSE).

**Background**

Evaluation of abnormalities of left ventricular (LV) function from wall thickening during DSE is unsatisfactory and requires a high level of expertise.

**Methods**

In 10 open-chest anesthetized pigs, myocardial deformation was studied before and during dobutamine infusion, under control and ischemic conditions produced by various degrees of coronary artery constriction: 2 of nonflow-limiting stenoses (NFLS) of increasing severity reducing left anterior descending artery hyperemic flow by 40% and 70% and 2 flow-limiting stenoses (FLS) reducing resting coronary flow by 25% and 50%. Agreement between 2D strain echocardiography and sonomicrometry (reference method) was evaluated by linear regression and Bland-Altman analysis.

**Results**

Good correlation and agreement were observed between 2-dimensional strain and sonomicrometry at rest and during dobutamine infusion; longitudinal strain: \( r = 0.77, p < 0.001 \) and \( r = 0.80, p < 0.001 \); radial strain: \( r = 0.57, p < 0.05 \) and \( r = 0.63, p < 0.05 \); and circumferential strain: \( r = 0.74, p < 0.001 \) and \( r = 0.58, p < 0.001 \). Circumferential and longitudinal strains in the risk area were significantly decreased at rest in the presence of FLS and during dobutamine infusion in the presence of NFLS. By contrast, radial strain was significantly decreased in the presence of severe FLS only during dobutamine infusion.

**Conclusions**

The 2D strain provides accurate assessment of LV regional function. Evaluation of circumferential and longitudinal strains during DSE has real potential for quantitative evaluation of LV deformation in the routine assessment of ischemia. (J Am Coll Cardiol 2008;51:149–57) © 2008 by the American College of Cardiology Foundation
Ten male York pigs, weighing between 30 and 45 kg with the Guide for the Care and Use of Laboratory Animals. The experimental protocols complied during DSE in pigs.

**Methods**

**Animal preparation.** The experimental protocols complied with the Guide for the Care and Use of Laboratory Animals (13). Ten male York pigs, weighing between 30 and 45 kg (38 ± 3 kg) and free of clinically evident disease, were used for this study. Each animal was sedated with an intramuscular injection of 20 mg/kg ketamine hydrochloride plus acepromazine (1 ml) and anesthetized with sodium pentobarbital (10 mg/kg). A slow intravenous infusion of saline maintained hydration throughout the surgery, and anesthesia was maintained by continuous intravenous perfusion of ketamine (500 mg/h). Rectal temperature was monitored and kept constant at 37.5°C to 38.6°C using a fluid-filled heating pad. The trachea was intubated through a midline incision in the LV anterior wall.

On the basis of these considerations, we explored the potential of 2-dimensional strain for the detection of ischemia during DSE in pigs.

**Assessment of contraction by sonomicrometry.** For the sonomicrometric measurements, a Sonometrics digital ultrasonic measurement system (Sonometrics Corp., London, Ontario, Canada) was used. Three pairs of segment-length ultrasonic crystals (2 mm) were inserted via a small scalpel incision in the LV anterior wall.

To investigate RS, a first pair of crystals was placed and sutured, 1 crystal in the inner layer (placed obliquely to avoid damage to the myocardium under study) and another crystal in the outer layer of the LV anterior wall. To analyze LS, a second pair of crystals was positioned parallel to the long axis of the LV. For CS assessments, a third crystal pair was placed perpendicular to the long axis of the LV. The longitudinal, circumferential, and radial peak systolic strains were obtained by calculation of the instantaneous distance between crystals normalized to the end-diastolic length. Sonomicrometric data were acquired immediately before the echocardiographic data and then switched off during echocardiographic data acquisition.

**Assessment of contraction by echocardiography.** A Vivid 7 (GE Medical Systems, Horten, Norway) was used to acquire echocardiographic data with a 4-MHz transducer placed directly on the epicardium. The transducer was fixed in a saline-filled latex bag. B-mode second harmonic images (mean frame rate = 75 Hz) were recorded in parasternal, apical 4-chamber, apical 2-chamber, and apical 3-chamber views. The imaging planes were matched to the crystal positions by direct echocardiographic visualization of the crystals inserted into the wall. The data were stored and transferred to a computer for postprocessing analyses. The recordings were analyzed with Echopac software (GE Medical Systems). The CS, RS, and WT were obtained in the parasternal short-axis view. Apical views were used to measure LS in the risk (RA, anterior wall) and control areas (CAs) (inferolateral wall). Echocardiographic analysis consisted of measurement of the peak of strain in the end-systolic phase within the RA and the CA. Figure 1 shows an example of peak CS in RA and in CA in the absence (panel A) and presence of coronary stenosis (panel B).

**Experimental protocol.** Figure 2 shows the different stages of the protocol. After baseline evaluation, 4 stages of ischemia of increasing severity were applied: 2 stages of nonflow-limiting stenoses (NFLS) and 2 stages of flow-limiting stenoses (FLS). The NFLS were set to obtain reductions of LAD flow in hyperemia (obtained by 140 μg/kg/min adenosine infusion) by 40% and 70%, respectively. FLS were set to obtain reductions of LAD baseline resting flow by 25% and 50%, respectively. Aortic pressure, LAD flow, and sonomicrometric and echocardiographic data were obtained for each stage (baseline and...
the 4 ischemia stages) before and after a 15-min period of continuous intravenous dobutamine infusion (30 μg/kg/min).

After the end of dobutamine infusion, the animals were allowed to return to resting conditions (30 min). The animals were sacrificed at the end of the experiment while they were under deep anesthesia.

Statistical analysis. Data were expressed as means ± standard deviation. Statistical analysis was performed with StatEl software (ad Science, Paris, France). The agreement between sonomicrometry and 2D strain was assessed by linear regression analysis and the Bland and Altman method (14). The intraclass correlation coefficient (ICC) was calculated as a measure of consistency between the 2D strain and sonomicrometry. Hemodynamic and echocardiographic measurements were compared by a paired Student t test and when necessary by the Mann and Whitney test. A p value of <0.05 was considered significant.

Results

Hemodynamic data. Basic hemodynamic parameters obtained during the experimental conditions are summarized in Table 1. Induction of NFLS or FLS did not induce any significant changes in heart rate or blood pressure. Infusion of dobutamine was systematically followed by a significant increase in heart rate (mean, approximately +24%, p < 0.05) and systolic blood pressure (approximately +17%, p = NS), and this effect occurred to the same extent with or without coronary artery stenosis. Dobutamine also induced a significant increase in coronary flow, but this effect was more pronounced in the absence than in the presence of coronary artery stenosis (+100%, +92%, +60%, +62%, and +48% in the absence and in the presence of NFLS 40%, NFLS 70%, FLS 25% and FLS 50%, respectively).

Validation of 2D strain. The data obtained under all experimental conditions were pooled to evaluate the agreement between the 2 techniques, 2D strain and sonomicrometry. Figures 3 to 5 display linear regression analyses (panels A, C, and E) and Bland and Altman analyses (panels B, D, and F) between 2D strains and sonomicrometry for LS, RS, and CS pooled (at rest during dobutamine infusion), at rest and during dobutamine infusion. Good correlation and agreement were observed between the 2D strain echocardiographic and sonomicrometric data pooled at rest during dobutamine infusion, at rest, and during dobutamine infusion for LS (r = 0.81, p < 0.001, ICC = 0.95; r = 0.77, p < 0.001, ICC = 0.96 and r = 0.80, p < 0.001, ICC = 0.93, respectively), RS (r = 0.61, p < 0.01, ICC = 0.98; r = 0.57, p < 0.05, ICC = 0.98 and r = 0.63, p < 0.05, ICC = 0.98, respectively), and CS (r = 0.69, p < 0.001, ICC = 0.62; r = 0.74, p < 0.001, ICC = 0.73 and r = 0.58, p < 0.001, ICC = 0.50, respectively).

Intraobserver and interobserver variability was measured by calculating the ratio of the mean difference between 2 measurements over the mean of those measurements.
Effects of ischemia and dobutamine on strain. Figure 6 summarizes the measurements of myocardial strain obtained by 2D strain and WT evaluation in RA and CA before and after infusion of dobutamine with and without ischemia.

During control conditions (no ischemia), dobutamine infusion significantly increased CS by 16.5% ± 18%, LS by 23% ± 21%, RS by 55% ± 45%, and WT by 44% ± 13%, and these same effects were seen in the sonomicrometric measurements.

At rest, induction of NFLS 40% and NFLS 70% tended to reduce CS and LS in RA without reaching significance. FLS 25% significantly reduced LS (approximately −27%, p < 0.05), and FLS 50% reduced CS (approximately −26%, p < 0.05). RS was not significantly reduced at rest.

Dobutamine stress echocardiography detected abnormalities in strain in RA during ischemic conditions. The effects of coronary artery stenosis on the different strains were more pronounced during dobutamine infusion. The NFLS 40% did not induce any significant changes in the different strains, NFLS 70% induced significant reduction in LS (approximately −17%, p < 0.05) and CS (approximately −17%, p < 0.05) but not in RS. FLS 50% significantly decreased LS (approximately −39%, p < 0.01), CS (approximately −26%, p < 0.05), RS (approximately −28%, p < 0.05), and WT (approximately −29%, p < 0.05).

In summary, decreases in LS and CS were observed at an earlier stage of ischemia than those in RS.

Reproducibility. The intraobserver and interobserver variabilities for the different 2-dimensional strain values are listed in Table 2. The largest difference was observed for RS during dobutamine infusion.

Discussion

This experimental study was designed to find out if assessment of 2D strain could detect contraction abnormalities induced by ischemia. The ultimate aim was to determine its potential for diagnosis of coronary artery disease in man. We investigated the effects of acute coronary artery constriction in pigs subjected to dobutamine-induced stress. Our main findings were 2D strain was as reliable as sonomicrometry for detection of myocardial contraction abnormalities under both baseline and ischemic conditions at rest and during dobutamine infusion and CS and LS detected coronary stenoses at an earlier stage than did RS both at rest and during dobutamine challenge.

Over the past decade, dobutamine echocardiography has become an essential tool in the management of patients with suspected coronary artery disease. Its reliability is comparable to that of nuclear magnetic investigation with a higher access level and at a lower cost (15). However, this technique requires considerable experience, as demonstrated by differences in sensitivity and specificity between novices and experienced operators (1). This real limitation stems from the fact that this method is based on a qualitative analysis of
wall contraction abnormalities. The reliability and reproducibility of stress echocardiography has been improved by the advent of quantitative techniques. For instance, the speckle tracking method automatically obtains deformation measurements in the 3 main axes based on pure gray-scale ultrasound imaging.

In the present study, good agreement was found between 2-dimensional strain and sonomicrometric data. LS, CS, and RS components were estimated almost simultaneously and compared between rest and stress situations. Several experimental studies have validated 2D strain echocardiographic techniques (with sonomicrometry) during dobutamine infusion (9,11) or during ischemia (10–12). However, in these studies, the ischemia consisted of an acute coronary occlusion and not coronary stenoses of different severities in the present study, and dobutamine was not infused during the ischemic condition but was evaluated separately.

In clinical studies, 2D strain has been evaluated for distinguishing transmural from nontransmural infarction (16,17). More recently Ingul et al. (18) investigated myocardial deformation during DSE in 197 patients by automated analysis and concluded that this technique was feasible and accurate and could enhance sensitivity in the hands of expert investigators. Automated deformation was based on velocity gradient and segment length methods of measuring longitudinal motion within a region of interest tracked through the cardiac cycle. Both methods had comparable sensitivities and specificities that were superior to conventional reading. To our knowledge, the present experimental study is the first to simultaneously assess the 3
different strain components during stress echocardiography in the presence of different extents of coronary stenosis.

We feel that 2D strain represents a better parameter than WT for early detection of myocardial contraction abnormalities during DSE. The 2D strain can evaluate longitudinal or circumferential abnormalities, which precede the decrease in radial deformation in ischemia. Since subendocardial myocardial fibers, which are mainly longitudinally oriented, are more susceptible to ischemia, it might be expected that the longitudinal function is altered earlier than the radial function (as assessed by the WT parameter) (19,20). This could explain why LS decreased at lower degrees of coronary constriction and probably at lower doses of dobutamine than did RS. The distribution of myocardial fibers within the wall has clinical implications for quantifying inducible ischemia during DSE. Myocardial deformations should perhaps be explored independently in the different LV myocardial layers (subepicardial, midendocardial, and subendocardial).

**Study limitations.** In this study, the acute induction of a coronary artery constriction is not truly representative of the chronic progression of coronary artery disease in humans, in which adaptive processes such as LV remodeling, collateral flow, and angiogenesis take place. Nevertheless, changes in LV deformation were assessed under dobutamine-induced stress in a manner similar to that employed in routine clinical practice. Although such differences might have affected the extent of the stress-induced modifications, they were unlikely to have affected the sonomicrometric and 2D strain measurements differently.

![Figure 4](image-url)

**Figure 4** Comparison of Radial 2D Strain With Sonomicrometry Under Control and Ischemic Conditions at Rest and After an Intravenous Infusion of 30 μg/kg/min Dobutamine

(A) Linear regression analysis of pooled data (at rest + after intravenous infusion of 30 μg/kg/min dobutamine). (B) Bland-Altman analysis of pooled data (at rest + after infusion of dobutamine). (C) Linear regression analysis at rest. (D) Bland-Altman analysis at rest. (E) Linear regression analysis after dobutamine infusion. (F) Bland-Altman analysis after dobutamine infusion.
Stage levels were defined by coronary flow reduction, which could be different than myocardial perfusion. However, our model has been previously validated using microspheres (21).

There are significant changes in regional and global mechanics after opening the pericardium. The numeric values and the pattern of changes may be different in closed-chest models and humans.

The frame rate used for the ultrasound data was 70 to 80 Hz. A high temporal resolution is required for high heart rates, such as during DSE. This could explain why the intraobserver and interobserver variabilities were lower during the dobutamine infusion, when heart rate increased to 150 to 155 beats/min.

The reproducibility of 2D RS was lower than that for LS or CS, as previously observed (22). This could be partly explained by the larger amplitude of this strain compared with the other 2 and possibly also by the capacity of the software in this axis.

The number of comparative values was less for RS than for LS or CS, as we have found it more difficult to obtain a good signal for the sonomicrometric evaluation of RS (Figs. 2 to 4). Such difficulties have also been noted by Korinek et al. (10).

Although variations between echocardiographic evaluation and sonomicrometry could be partly explained by misalignment between the ultrasound plane and the crystals, we took care to keep the ultrasound crystals...
Conclusions

The 2D strain is a new technique with real potential for quantitative evaluation of myocardial function. During DSE under ischemic conditions, abnormalities in CS and LS were detected before radial dysfunction, and thus they provide an earlier indication of coronary stenosis. Clinical studies with 2-dimensional strain during DSE are needed to confirm these experimental findings.

**Variabilities of Myocardial Strain Measurement by 2-Dimensional Strain**

<table>
<thead>
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<th>Longitudinal Strain</th>
<th>Circumferential Strain</th>
<th>Radial Strain</th>
<th>Mean Strain Variation</th>
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<tr>
<td>Rest</td>
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<td>11%</td>
<td>10%</td>
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<tr>
<td>Dobutamine</td>
<td>10%</td>
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<td>15%</td>
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<tr>
<td>Interobserver</td>
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There was higher variability for radial than for longitudinal or circumferential strains and more variability during dobutamine infusion than under resting conditions.

Figure 6  Myocardial Strains Measured by 2D Strain in RA and CA at Rest and During Dobutamine Stress

*p < 0.05 versus no stenosis (base); p < 0.05 versus rest. CS = circumferential strain (in %); LS = longitudinal strain (in %); RS = radial strain (in %); WT = wall thickening (in %); other abbreviations as in Figure 2.
REFERENCES


