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Quantitative Assessment of Intrinsic Regional Myocardial Deformation by Doppler Strain Rate Echocardiography in Humans

Validation Against Three-Dimensional Tagged Magnetic Resonance Imaging

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Background—Tissue Doppler echocardiography–derived strain rate and strain measurements (SDE) are new quantitative indices of intrinsic cardiac deformation. The aim of this study was to validate and compare these new indices of regional cardiac function to measurements of 3-dimensional myocardial strain by tagged MRI.

Methods and Results—The study population included 33 healthy volunteers, 17 patients with acute myocardial infarction, and 8 patients with suspected coronary artery disease who were studied during dobutamine stress echocardiography. Peak systolic myocardial velocities were measured by tissue Doppler echocardiography, peak systolic strain rates and strains by SDE, and strains by tagged MRI. In healthy individuals, longitudinal myocardial Doppler velocities decreased progressively from base to apex, whereas myocardial strain rates and strains were uniform in all segments. In patients with acute infarction, abnormal strains clearly identified dysfunctional areas. In infarcted regions, SDE showed $1.5 \pm 4.3\%$ longitudinal stretching compared with $-15.0 \pm 3.9\%$ shortening in remote myocardium ($P < 0.001$), and radial measurements showed $-6.9 \pm 4.1\%$ thinning and $14.3 \pm 5.0\%$ thickening ($P < 0.001$), respectively. During dobutamine infusion, longitudinal strains by SDE increased significantly from -13.5% to -23.8% ($P < 0.01$) and radial strains increased from $13.1 \pm 3.1\%$ to $29.3 \pm 11.5\%$ ($P < 0.01$). Comparisons between myocardial strains by SDE and tagged MRI in healthy individuals ($n=11$), in infarct patients ($n=17$), and during stress echo ($n=4$) showed excellent correlations ($r=0.89$ and $r=0.96$ for longitudinal and radial strains, respectively, $P < 0.001$).

Conclusions—The present study demonstrates the ability of Doppler echocardiography to measure myocardial strains in a clinical setting. Myocardial strains by Doppler may represent a new powerful method for quantifying left ventricular function noninvasively in humans. (*Circulation*. 2002;106:50-56.)

Key Words: echocardiography ■ magnetic resonance imaging ■ myocardium ■ contractility

Accurate identification of regional myocardial dysfunction is pivotal to the diagnosis and management of patients with coronary artery disease. However, present methods for the assessment of regional myocardial function rely on semiquantitative visual gradation of endocardial excursion and wall thickening and are therefore highly subjective.^{1,2} In addition, visual assessment cannot easily distinguish the contribution of rigid body translational motion affecting the entire heart from regional contractility, nor can it differentiate wall motion abnormalities generated by passive tethering from those caused by active intrinsic contraction.

Tissue Doppler imaging (TDI) recently has been introduced as a method to quantitatively assess regional myocardial function by providing a map of color-encoded tissue velocities.³⁻⁸ TDI offers no solution, however, to the issue of

distinguishing local velocity from translational motion and tethering effects from other regions. A potentially more specific measure of regional function would be quantification of regional deformation or strain. The concept of myocardial strain was defined by Mirsky and Parmley⁹ as fractional tissue deformation in response to applied force (stress). Quinones et al¹⁰ suggested measuring myocardial strain rate from M-mode echocardiographic data, but this principle has not been implemented in clinical routine. More recently, Heimdal et al¹¹ introduced TDI-derived real-time strain rate, from which regional myocardial strain may be derived as the time integral of regional Doppler velocity gradients.¹²

In principle, myocardial strains are independent of translational motion and other through-plane motion effects and should be relatively uniform throughout the normal left ventricular (LV) myocardium. In contrast, myocardial veloc-

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ities show marked nonuniformity in the normal ventricle, and this complicates data interpretation. The assessment of myocardial strain by tissue Doppler imaging (SDE) could simplify the analysis of regional contractile function by providing a more objective and uniform parameter of myocardial function. However, the validity and relevance of this novel parameter has not been established clinically. Therefore, the aim of the present study was to validate the measurements of peak systolic myocardial strains from regional velocity gradients against strains obtained by 3-dimensional tagged MRI. Additionally, we sought to compare the regional distribution of myocardial strains to that of regional myocardial velocities to establish which parameter might be more useful for clinical assessment of regional contractility.

Methods

Study Population

Three groups of subjects were studied. Thirty-three healthy volunteers (24 men, 9 women, 41 ± 13 years of age) and 17 patients (11 men, 6 women, 56 ± 15 years of age) with recent acute myocardial infarction (10 anterior and 7 inferior) were studied during resting conditions. Eleven volunteers and all infarct patients underwent both SDE and magnetic resonance tagged-cine imaging within the same day, typically with <2 hours between both investigations. In addition, 8 patients (4 men, 4 women, 65 ± 12 years of age) with suspected coronary artery disease were studied by SDE both at rest and during maximum dose of dobutamine infusion while undergoing a dobutamine stress echo mandated clinically to evaluate chest pain. β -Blockers (3 subjects) were withdrawn 24 hours before the study. Four of the subjects agreed to repeat the dobutamine stress test with the use of MRI on a separate day, having had no changes in medication regimen and clinical status in the meantime. The Institutional Review Board of the Johns Hopkins University approved the study protocol, and all subjects gave informed written consent to participate in this study.

Echocardiography

All studies were acquired with the use of a System Five digital ultrasound scanner (GE Medical Systems). After views were optimized in fundamental mode, images were acquired in TDI mode. Both myocardial velocities and strain values could be assessed from the same heartbeat. Frame rates varied from 56 to 134 frames per second, with a mean value of 92. Analysis of SDE and TDI images was performed offline on a personal computer with the aid of a customized software package (Echopac, GE Medical Systems). For tissue velocity measurements, we used a 2-dimensional multiregion technique, which allowed simultaneous processing of multiple velocity traces as described earlier.¹³ Peak systolic myocardial velocity was assessed from the apical, mid, and basal segments, using the same regions as for strain measurements.

From tissue Doppler data, incremental strain rate (SR) can be estimated by calculating the velocity gradient¹², as follows:

$$(1) \quad SR \approx \frac{v(r) - v(r + \Delta r)}{\Delta r},$$

where v is the tissue velocity at different range depths r . The time integral of incremental strain rate yields logarithmic strain $e = \log(L/L_0)$:

$$(2) \quad e = \log \left(\frac{L}{L_0} \right) = \int_{t_0}^t SR \, dt,$$

where L is the instantaneous segment length and L_0 is the segment length at time t_0 . In this study, the logarithmic strain was converted to Lagrangian strain $\epsilon = (L - L_0)/L_0$:

$$(3) \quad \epsilon = \frac{L - L_0}{L_0} = \exp(e) - 1.$$

The velocity gradient was estimated between two points (r and $\Delta r + r$) with a distance of 8 mm. This spatial offset (Δr) was selected as a compromise between acceptable signal-to-noise ratio and longitudinal spatial resolution.

MRI Tagging

MRI was performed on a 1.5-T whole-body magnet (Signa, GE Medical Systems) with a phased-array cardiac coil. Tagged images were acquired with the use of an ECG-triggered segmented k-space fast gradient-echo sequence with spatial modulation of magnetization (DANTE-SPAMM) during breath holds. Four to 5 contiguous stacks of short-axis images were prescribed to cover the entire heart from base to apex. From these short-axis slices, 6 long-axis slices were prescribed radially every 30 degrees. Imaging parameters were as follows: tag separation, 7 mm; field of view, 36 cm; slice thickness, 8 mm; matrix size, 256×160 ; TR, 6.2 ms; TE, 2.3 ms; and flip angle, 15 degrees.

Dobutamine Stress

Similar dobutamine stress tests were performed in the echocardiographic laboratory and in the MRI environment. ECG was monitored continuously, and blood pressure was recorded every 3 minutes throughout the procedure. After baseline acquisitions, dobutamine was increased stepwise by $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ every 3 minutes, using a standard protocol up to $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or until 85% of maximal predicted heart rate was reached. Full SDE and 3-dimensional MRI sets were acquired at baseline and at peak dobutamine stress.

Coregistration of Myocardial Strains by Both Techniques

Analysis of 3-dimensional strains from tagged MRI data sets was performed with a displacement field-fitting method to estimate the Lagrangian strain.¹⁴ Strains by MRI were computed in the 3 normal orthogonal directions (radial, circumferential, and longitudinal) and reported as a strain map consisting of 12 circumferential angular sectors and 4 to 5 longitudinal planes. They were expressed as percent change in segment length between end-diastole and end-systole.

Longitudinal strains were obtained by SDE with apical 4- and 2-chamber views, respectively, and were compared with longitudinal shortening strain by MRI from the same segments. The midmyocardial layer was chosen from both methods. From the parasternal short-axis view, we measured radial strains by SDE in the anteroapical and posterior walls. Two different investigators unaware of each other's results analyzed MRI tagging and Doppler measurements.

Statistical Analysis

Values are expressed as mean $\pm$ SD. Comparisons between peak systolic strain values by SDE and MRI were performed by linear regression analysis. Differences between myocardial peak systolic strains, strain rates, and velocities in each myocardial segment were analyzed with 2-way ANOVA methods. Comparisons of myocardial peak systolic strains, strain rates, and velocities at baseline and peak dose of dobutamine were analyzed with paired Student's t tests. The agreement between the 2 methods (peak systolic strain by MRI and Doppler) was expressed as 95% limits of agreement, as recommended by Bland and Altman.^{14a} A value of $P < 0.05$ was considered statistically significant.

Results

Healthy Volunteers

Typically, normal LV myocardium shortens in the longitudinal direction and thickens along the radial direction during systole. Because SDE records intrinsic deformation of the

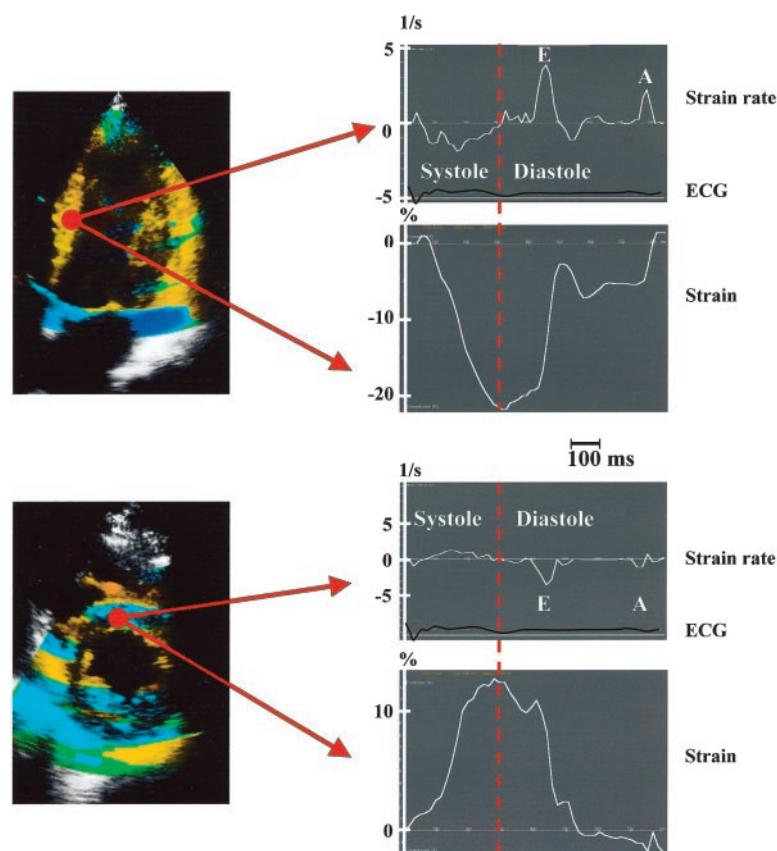


Figure 1. Top left, Systolic strain rate image recorded from an apical 4-chamber view in a healthy volunteer. The uniformly yellow color in the LV indicates longitudinal compression. Top right, Longitudinal strain rates and strains in a midseptal region. Bottom, Systolic short-axis strain rates and strains. The blue color in the LV anterior and posterior wall indicates systolic thickening.

myocardium only along the orientation of the Doppler beam, longitudinal shortening is measured from apical views. Shortening or thinning strains and strain rates (ie, compression) are by convention shown by negative signs. Thickening or lengthening strains and strain rates (ie, expansion) are shown with positive signs. An example of an apical 4-chamber and a parasternal short-axis SDE image with corresponding strain rates and strains obtained in a healthy volunteer is shown in Figure 1. In short-axis views, myocardial shortening is perpendicular to the direction of the Doppler beam and, therefore, SDE measurements of strains in the anteroseptal and posterior walls reflect radial thickening (lower right panel). Mean values of Doppler strain and strain rate in the healthy volunteers are reported in Tables 1 and 2.

Figure 2 illustrates the distributions of regional myocardial velocities by TDI and strains by SDE in healthy volunteers. Longitudinal tissue velocities were heterogeneously distrib-

uted in the normal LV, showing progressive decrease from the base toward the apex, mainly attributable to the through-plane motion of the heart. By contrast, values of myocardial strain and strain rate were found to be relatively homogeneous in all regions of the heart, reflecting independence from rigid body motion of the entire heart. Peak negative systolic longitudinal strains from all longitudinal segments assessed by both methods were $-18.7 \pm 3.7\%$ by SDE and $-18.1 \pm 3.6\%$ by MRI (Tables 1 and 2). Peak systolic radial strains were $18.0 \pm 5.3\%$ and $17.8 \pm 7.5\%$. The ranges of strain values in healthy subjects were -9 to -30% and -9% to -28% by SDE and MRI, respectively.

Regional Myocardial Deformation in Postinfarct Patients

In contrast to normal hearts, the left ventricle of postinfarct patients was characterized by marked nonuniformity of myo-

TABLE 1. Myocardial Velocities, Strain Rates, and Strains in Healthy Volunteers: Longitudinal Measures From 8 Segments (2- and 4-Chamber Views)

	Segments							
	Anterior		Septal		Posterior		Lateral	
	Base	Apex	Base	Apex	Base	Apex	Base	Apex
Tissue Doppler velocities, cm/s (n=33)	6.5 ± 1.6	$2.8 \pm 1.0^*$	6.7 ± 1.4	$2.8 \pm 1.1^*$	6.5 ± 1.4	$2.9 \pm 1.3^*$	6.7 ± 1.5	$3.2 \pm 1.6^*$
Doppler strain rate, 1/s (n=33)	-1.7 ± 0.4	-1.6 ± 0.4	-1.6 ± 0.4	-1.7 ± 0.3	-1.6 ± 0.3	-1.7 ± 0.3	-1.6 ± 0.3	-1.6 ± 0.3
Doppler strain, % (n=33)	-19 ± 4	-18 ± 5	-17 ± 3	-19 ± 4	-20 ± 4	-21 ± 2	-18 ± 4	-17 ± 3
MRI strain, % (n=11)	-17 ± 3	-18 ± 4	-17 ± 3	-19 ± 5	-18 ± 4	-19 ± 3	-18 ± 4	-17 ± 4

TABLE 2. Myocardial Velocities, Strain Rates, and Strains in Healthy Volunteers: Radial Measures From 2 Segments (Parasternal Short-Axis View)

	Segments	
	Anterior	Posterior
Tissue Doppler velocities, cm/s (n=33)	-3.5 ± 0.8	4.4 ± 0.6
Doppler strain rate, 1/s (n=33)	1.6 ± 0.2	1.8 ± 0.4
Doppler strain, % (n=33)	18 ± 6	18 ± 9
MRI strain, % (n=11)	19 ± 4	17 ± 6

* $P < 0.05$ vs the basal segment within the same region.

cardial systolic strains (Table 3). This is illustrated in Figure 3, which displays myocardial strains from an infarcted region. In the longitudinal direction, both SDE and MRI demonstrated reduced shortening or stretching in infarcted segments ($1.5 \pm 4.3\%$ and $0.4 \pm 4.9\%$, respectively). This was in contrast to the nonischemic region, where near-normal shortening was observed ($-15.0 \pm 3.8\%$ and $-15.7 \pm 3.6\%$ by Doppler and MRI, respectively). The ranges of longitudinal strain values in ischemic myocardium were -8% to $+11\%$ and -9% to $+10\%$ by SDE and MRI, respectively.

In the short-axis view, instead of apparently normal radial thickening strain as found in remote noninfarcted myocardium ($14.3 \pm 5.0\%$ and $15.1 \pm 6.0\%$), infarcted segments demonstrated marked reduction in thickening or systolic thinning ($-6.9 \pm 4.1\%$ and $-5.3 \pm 4.4\%$ by both SDE and MRI, respectively).

Alterations of Intrinsic Deformation During Dobutamine Stress

The maximum dobutamine dose reached during the stress test was $41 \pm 9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (range, 20 to 50). Atropine (1 mg) was given to 1 patient to additionally increase heart rate. Dobutamine infusion significantly increased heart rate from 72 ± 13 to 121 ± 16 bpm ($82 \pm 16\%$ of maximal predicted heart rate, $P < 0.001$) and tended to increase systolic blood pressure (from 118 ± 16 to 157 ± 59 mm Hg; not significant). Longitudinal shortening and radial thickening increased significantly between baseline and dobutamine infusion, illustrating the

TABLE 3. Peak Systolic Strains in Patients With Myocardial Infarction (n=17)

Region	Radial Thickening, %		Longitudinal Shortening, %	
	SDE	MRI	SDE	MRI
Anterior infarct (n=10)				
Infarct	-5.9 ± 3.3	-4.6 ± 4.5	1.1 ± 4.5	1.0 ± 4.7
Remote	10.0 ± 3.4	12.5 ± 7.9	-15.1 ± 3.5	-15.3 ± 3.6
Posterior infarct (n=7)				
Infarct	-9.2 ± 5.1	-6.8 ± 4.3	2.3 ± 3.9	0.8 ± 5.2
Remote	16.4 ± 4.2	16.3 ± 4.6	-14.9 ± 4.3	-16.2 ± 3.9

positive inotropic effect of this drug. Changes in maximal end-systolic strain from longitudinal view by SDE and MRI during dobutamine infusion were from -13.5 ± 3.1 to $-23.8 \pm 4.2\%$ ($P < 0.05$) and from -12.5 ± 4.8 to $-20.5 \pm 2.9\%$ ($P < 0.01$), respectively.

Correlations and Agreement Between Strains Assessed by SDE and MRI Tissue Tagging

Figure 4 demonstrates correlations between longitudinal systolic strain measurements by tagged MRI and SDE in each group of patients and healthy subjects. The overall correlation between SDE and MRI for pooled measurement of myocardial strain in healthy volunteers, postinfarct patients, and during dobutamine infusion was excellent ($r = 0.92$ and $r = 0.84$ for radial and longitudinal strain, respectively; both $P < 0.001$). There were also good correlations within each group of study subjects.

Figure 5 shows a Bland-Altman plot of differences between strain values obtained from MRI and SDE in healthy subjects and patients with myocardial infarction. The mean difference ± 2 SD was 0.4 ± 6.8 , -0.7 ± 6.6 , and 0.4 ± 4.1 in healthy subjects, in patients with myocardial infarcts, and during stress echo, respectively. In the subgroup of healthy subjects, the regression data are calculated from strain values that are clustered over a very narrow range of strains. As indicated by the Bland-Altman plots in Figure 5, however, the

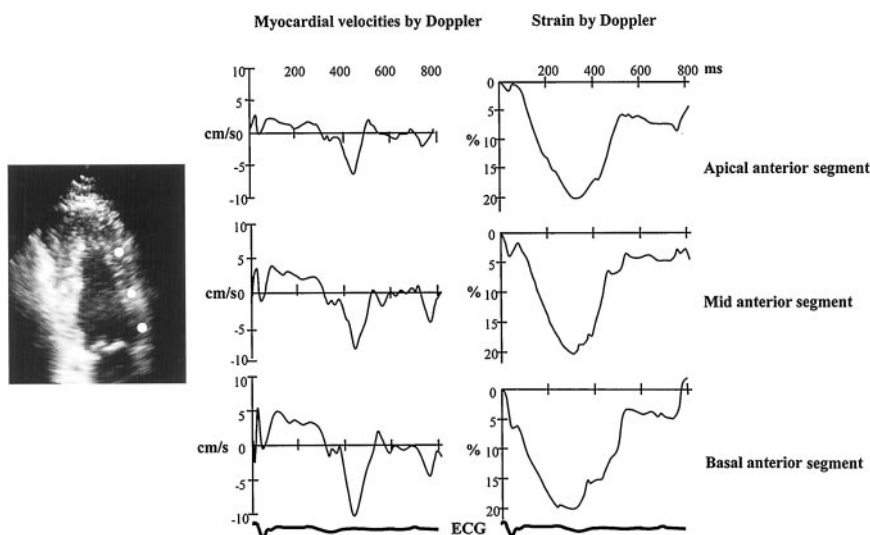


Figure 2. Comparison of myocardial Doppler velocities (left) and strains (right) by TDI. Measurements were performed simultaneously during the same heart-beat and captured from apical, mid, and basal segments (white dots) in the anterior wall. Myocardial velocities decrease from the base toward the apex, whereas myocardial strains are uniform along the long axis of the LV.

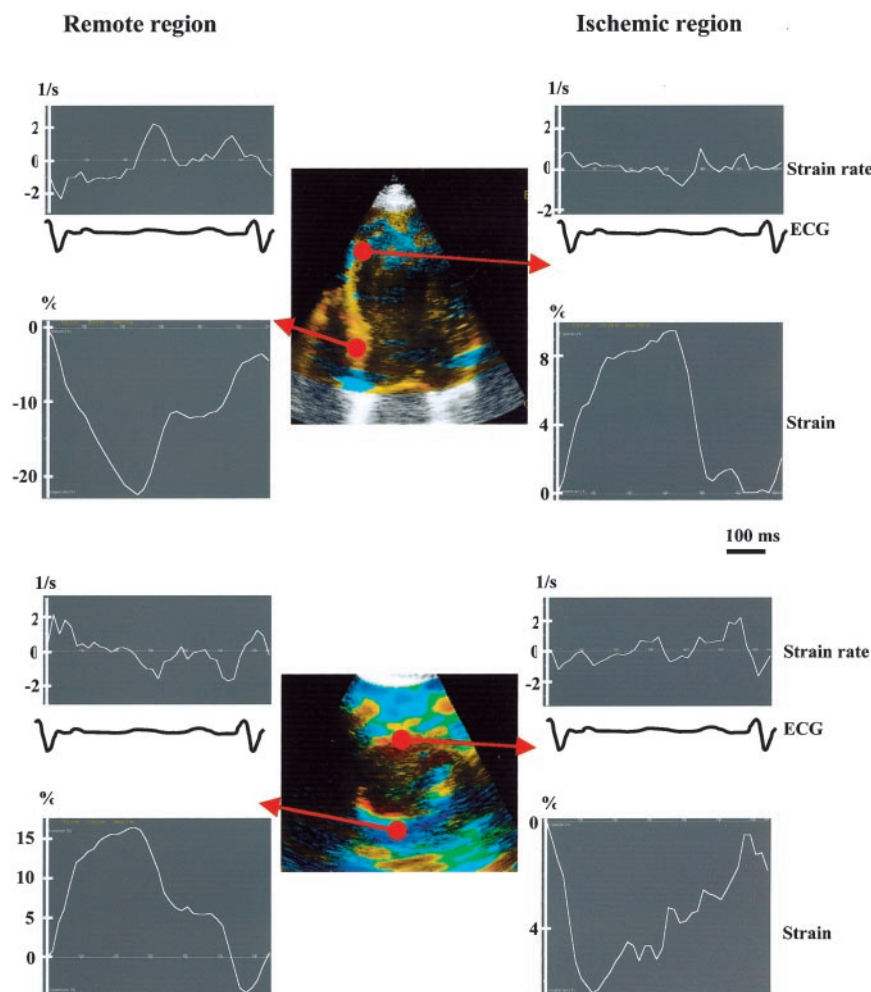


Figure 3. Systolic strain rate images and strain and strain rate traces in a patient with myocardial infarction. Top panels reproduce long-axis measurement, and the bottom panels reproduce short-axis measurements. The infarcted apical area demonstrates longitudinal expansion during systole as opposed to shortening within the remote area. The short-axis images demonstrate systolic thinning in the infarcted septal region.

agreement between the 2 methods in healthy subjects is similar to that in the patient groups.

Discussion

With tagged MRI as reference method, we have demonstrated the ability of strain Doppler echocardiography to quantify regional myocardial strains in a clinical setting, in all coronary perfusion territories and in patients with different degrees of myocardial function. In normal hearts, systolic strain values were essentially homogeneous throughout the left ventricle, which was in contrast to the distribution of myocardial velocities. The latter observation relates to the relative independence of strains from motions caused by tethering to other structures or cardiac translation.

Strain Versus Strain Rate

In principle, systolic strain reflects the extent of myocardial fiber shortening, whereas strain rate reflects velocity of shortening. Therefore, myocardial strain and strain rate reflect somewhat different aspects of myocardial function, and the 2 methods may provide complementary information.^{11,12,15} In the present study, both myocardial strains and strain rates were measured, providing detailed information about regional LV function within normal and ischemic myocardium in humans. The recent study by Greenberg et

al¹⁶ suggests that strain rate may be a sensitive marker of inotropy.

Strain Versus TDI

In opposition to tissue velocities, our study indicated that myocardial strains in the normal human heart, as measured by Doppler and MRI, were homogeneously distributed from base to apex of the LV. This difference relates to the fundamental difference between deformation and velocities and to the fact that the LV apex is relatively stationary during the cardiac cycle. Our observation is consistent with recent MRI studies showing uniformity of strains within different regions of the heart.^{17,18} This characteristic of myocardial strain reflects the fact that regional contractility of individual myocardial regions is relatively uniform and will facilitate the differentiation of normal from abnormal contractility in different regions of the heart. Conversely, the marked non-uniformity of myocardial velocities that showed a progressive decrease when moving the sample volume from the base toward the apex may limit the ability of TDI to separate normal from abnormal regions with the use of this parameter.¹⁹ Regional myocardial velocities are generated in part by local fiber shortening and in part by motion caused by tethering from other regions.¹² It remains to be determined, however, if these limitations of TDI are of clinical significance.

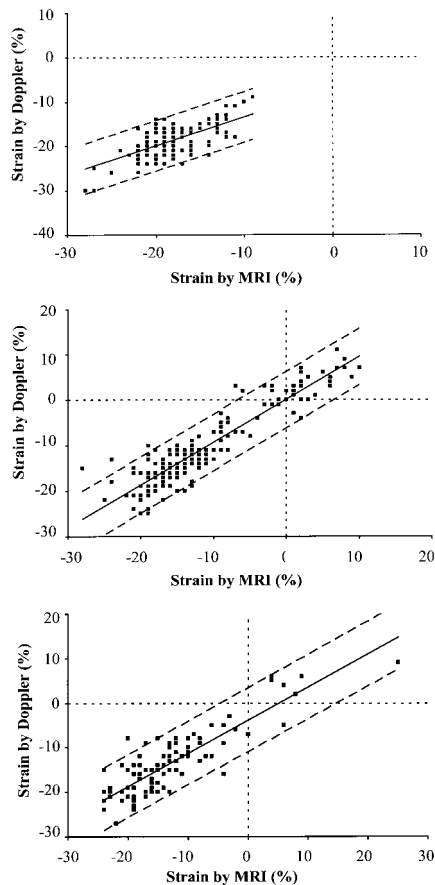


Figure 4. Scatter plot demonstrating correlations between systolic strain measurements by tagged MRI and SDE for longitudinal strain in healthy individuals ($y=0.65$ to 7.00 , $r=0.63$, $P<0.001$) (top), infarct patients ($y=0.94+0.14$, $r=0.93$, $P<0.001$) (middle), and dobutamine stress test patients ($y=0.74+3.78$, $r=0.87$, $P<0.001$) (bottom). For each patient, all myocardial segments are included in the analysis. Dotted lines, 95% confidence bands.

MRI Versus Doppler

The present study demonstrates the feasibility of Doppler-derived strain measurement in humans under different conditions and validates it against MRI as an independent gold standard. The MRI method relies on deformation of tag lines to assess strain in 3 dimensions. Both methods were used to calculate the Lagrangian strain value from a given region of interest.^{12,14}

The first validation of the SDE-derived strain measurement was performed in an animal model and compared SDE with sonomicrometry.¹² This experimental validation model was limited to one region per animal. The present study, however, extends the findings in animals to clinical imaging in humans. Furthermore, we demonstrate that SDE is accurate in all regions of the left ventricle and for strains in both longitudinal and radial directions.

Strain measurements by SDE are confined to a 1-dimensional space. The 3-dimensional MRI technique accounts for through-plane motion effects occurring perpendicularly to the imaging plane, whereas no such corrections could be applied for the SDE strain measurements. The longitudinal spatial resolution of SDE is related to the

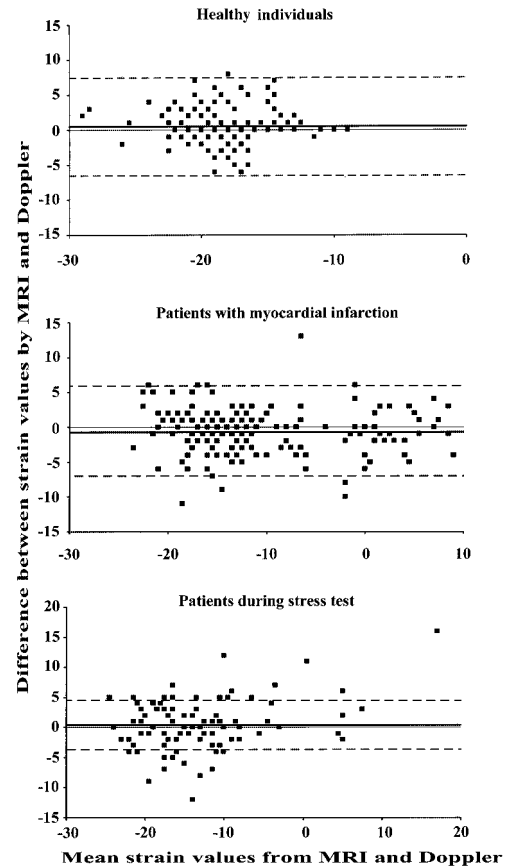


Figure 5. Bland-Altman plots of the difference between systolic strain values assessed by tagged MRI and SDE in healthy individuals (top), patients with myocardial infarction (middle), and patients during stress test (bottom). Dotted lines, mean ± 2 SD.

distance between the 2 sampling points for velocity gradient calculation. This offset was set to 8 mm as a compromise between demand for high spatial resolution and acceptable signal-to-noise ratio. In our experience, offsets <5 to 8 mm may give unacceptable noise levels in the strain rate signals. The present SDE method has very limited lateral resolution and in this regard is inferior to tagged MRI. Furthermore, the present Doppler method could hardly be used to measure longitudinal strains in different myocardial layers such as endocardium, myocardium, and epicardium. An improvement of the SDE acquisition technology with higher density of ultrasonic beams could make it possible to interpret the different cardiac layers in more detail.

Despite the fact that there are some differences in strains obtained from MRI and SDE, the limits of agreement between the techniques were relatively small, indicating that the impact of these potential errors is likely to be modest (Figure 5). Therefore, the present study gives foundation for the use of this technique to measure 3-dimensional strains in humans.

Clinical Implications

The results of this study suggest that quantitative measurement of myocardial strain by Doppler may provide an important advance over visual assessment of regional contractile function. For instance, SDE could be particularly

valuable to facilitate the interpretation of echocardiograms during stress. The exact place of SDE and TDI versus visual assessment of wall motion abnormalities, however, still has to be defined for stress echocardiography as well as for other clinical applications.

Deviation from normal function might be easier to define with SDE than TDI because of the homogeneity of strain measurements in normal myocardium. This would possibly result in greater specificity for this technique compared with TDI. Shortening strains in normal myocardium were between 9% and 30%. Shortening strains <9% were not found in any of the healthy individuals included in this study, which suggests that strains below this value are a marker of myocardial injury. We previously have demonstrated acceptable intraobserver and interobserver variabilities for strain measurements.¹³

Limitations

Like other Doppler modalities, strain measurements are dependent on the direction of the Doppler angle of incidence in relation to myocardial motion.¹² To overcome this limitation, longitudinal shortening was measured from long-axis views and radial thickening from short-axis views. For each segment, care was taken to keep the angle between the direction of the Doppler beam and that of tissue deformation as small as possible.

Strain profiles and curves do not always return to baseline (zero) at end-diastole. This may in part be because of the mathematical integration algorithm but may also be caused by the fact that the myocardium itself does not return to exactly the same state of deformation at the end of the cycle as was the case at the start. Several factors, including the normal beat-to-beat variation in stroke volume, may contribute to this.

Conclusions

The present study demonstrates the ability of tissue Doppler echocardiography to measure myocardial strains in a clinical setting and validates its accuracy against MRI tissue tagging. This novel technique may lead to improved noninvasive quantification of regional myocardial function in humans.

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