Assessment of Longitudinal and Radial Ventricular Dyssynchrony in Ischemic and Nonischemic Chronic Systolic Heart Failure: A Two-Dimensional Echocardiographic Speckle-Tracking Strain Study

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Background: Current guidelines recommend a QRS greater than or equal to 120 milliseconds to select candidates for cardiac resynchronization therapy. However, ischemic and nonischemic cardiomyopathies are two different entities and they might be selected following different approaches. We sought, thus, after a validation the new 2-dimensional (2D) speckle-tracking strain (STS) against color Doppler tissue imaging (DTI)-strain (S) to compare the different correlation between electrical and mechanical dyssynchrony (DYS) in ischemic and nonischemic cardiomyopathies.

Methods: We measured: (1) QRS duration; (2) mechanical interventricular DYS (the difference between preaortic and prepulmonary ejection times); (3) left intraventricular DYS (the SD of time-to-peak of longitudinal DTI-S); and (4) longitudinal and radial 2D-STS in the basal and middle segments of lateral and septal left ventricular walls in 95 patients with chronic heart failure caused by ischemic (n = 49) or nonischemic (n = 46) heart disease. Twelve healthy control subjects were also explored.

Results: Mechanical interventricular DYS was correlated (DTI-S: \( P < .001 \)) with QRS-duration, but not in ischemic heart disease. DTI-S and 2D-STS measurements were correlated (\( R = 0.6, P < .001 \)) in the overall population. Longitudinal 2D-S DYS was correlated with QRS duration in patients with nonischemic, (\( r = 0.48, P = .003 \), and \( r = 0.43, P = .003 \), respectively).

Conclusions: The profile of DYS is influenced by the underlying cause of heart failure. The 2D-STS is a new tool for cardiac DYS assessment. Its ability to measure both longitudinal and radial intraventricular DYS is noteworthy.

Recent practice guidelines issued by the European Society of Cardiology or the American College of Cardiology/American Heart Association for the diagnosis and treatment of chronic heart failure (HF) state that resynchronization therapy using biventricular pacing can be considered in patients with reduced left ventricular (LV) ejection fraction (EF) and ventricular dyssynchrony (DYS), manifest as a QRS duration greater than or equal to 120 milliseconds, who remain symptomatic (New York Heart Association [NYHA] III-IV) despite optimal medical therapy to improve symptoms, hospitalizations, and mortality.1,2 However, among all recipients of cardiac resynchronization therapy (CRT) systems, up to 30% do not respond to treatment.3,4 Furthermore, some patients with QRS duration less than 120 milliseconds who have distinct mechanical DYS might respond to CRT.5,6 Therefore, the substitution, or addition, of indices of mechanical DYS has been proposed to select candidates for CRT with greater accuracy.7 Assessment of mechanical DYS has consequently become a matter of great interest. Several imaging techniques and methods have been proposed to characterize and measure mechanical DYS, mainly Doppler echocardiography using M-mode, 2-dimensional (2D), or 3-dimensional imaging, and, above all, Doppler tissue imaging (DTI).7-12 These techniques have important technical limitations, remain difficult to apply widely in daily practice, and have not been validated in randomized prospective trials for the selection of CRT candidates.7,13

An analysis of regional function based on 2D speckle-tracking strain (STS), which offers a unique opportunity to gather information on regional deformation from a single gray-scale image in the longitudinal and radial directions, has recently been developed.14-16 However, applicability and clinical relevance of 2D-S remain unknown. Therefore, we sought to: (1) compare the contributions of 2D-STS versus DTI-strain (S) in the assessment of DYS in patients with chronic HF; (2) assess longitudinal and radial DYS in consecutive
patients with HF caused by ischemic or nonischemic heart disease; and (3) compare electromechanical correlates in the context of ischemic versus nonischemic heart disease. We assessed these correlations even in patients without current indication for CRT.

METHODS

The study enrolled 95 patients in chronic, stable, NYHA functional class II to IV with a LV EF of 40% or less, and a LV end-diastolic diameter of 55 mm or greater. In all, 11 patients were excluded from the analysis because of suboptimal echocardiographic images. Patients were selected for the study in stable, optimally pharmacologically treated, condition. None of the patients were congestive at the time of the echocardiographic examination. The study was in compliance with the rules of the ethics committee of our institution, and all patients gave their informed consent.

Twelve control subjects were analyzed in the same way.

Ischemic Versus Nonischemic Heart Disease

All patients underwent coronary angiography and a cause of the cardiomyopathy was defined according to the classification of Felker et al.17 Patients without coronary artery disease or with a single, less than 70% coronary artery stenosis were classified as having HF of nonischemic cause, unless the lesion was located on the left anterior descending or left main coronary artery. Patients with multiple coronary artery stenoses, or with high-grade stenoses of the left main or left anterior descending coronary arteries were classified as having HF caused by ischemic heart disease.

Electrical DYS

QRS duration was measured on a 12-lead surface electrocardiogram recorded at a speed of 50 mm/s. The duration of the widest QRS complex was used as the measurement of electrical DYS (in any of the leads).3

Echocardiographic Imaging

Transthoracic echocardiography was performed using a system (Vivid 7, GE VingMed, Milwaukee, WI) equipped with a 2.5-MHz phased-array transducer. A standard 4-window echocardiographic examination was performed. Apical 4- and 2-chamber views were acquired for calculation of the LV EF with the biplane method of disks. LV end-diastolic diameter was measured on a line drawn in the M-mode parasternal long-axis view. Pulsed Doppler was used to record right ventricular and LV outflow tract ejection flows. We recorded apical 4-chamber views in 2D gray-scale and color DTI, and stored S consecutive cardiac cycles on an optical disk for further analysis. The image sector was approximately 30 degrees, as narrow as possible to increase the frame rate to greater than 65 frames/s for the gray-scale imaging, and greater than 140 frames/s for DTI. Cineloops in color DTI and gray-scale imaging (harmonic) were stored. The gray-scale images were not retained if the epicardial and endocardial borders could not be traced for the 2D-STS analysis.

Calculation of 2D-STS

Using the original images, we performed offline measurements of S in the longitudinal and radial axes, using a dedicated software package (Echopac, General Electric, Horten, Norway), as described by Leitman et al.14 This system tracks acoustic markers within the myocardium, frame-by-frame, over one cardiac cycle. The spatial displacement of an acoustic marker indicates local tissue movement. A tracking setting was selected with a width between endocardium and epicardium to include as much myocardium as possible. The software automatically scores the tracking quality of each segment on a scale from 1.0, for optimal, to 3.0, for unacceptable. Segments with scores greater than 2.0 were excluded from the analysis. The tracking quality was verified visually to confirm the reliability of automatic tracking. The quality of the echocardiographic images was high enough to enable S analysis in 90% of segments. For each LV segment with sufficient tracking quality, longitudinal and radial S was calculated automatically and averaged over the whole segment.

For each basal and midventricular segment analyzed, the time to peak systolic S was measured on apical views, using the maximal negative S after the QRS for longitudinal, and the maximal positive S after the QRS for radial, S analysis. The same protocol was followed on the same apical views for the measurement of time to peak of S by DTI. The measurements of S by DTI and by 2D-STS were performed in the: (1) midportion of the basal segment of the septal and lateral LV walls; and (2) upper portion of the midsegment of the same LV walls.

We did not consider postystolic shortening for the analysis. In case of postystolic shortening, the systolic measurable peak was measured.

Assessment of Interventricular and Intraventricular Mechanical DYS

Interventricular DYS was assessed by the time interval between preaortic and prepulmonary ejection times, as previously described.18 Intraventricular DYS was assessed as the time delay between the earliest and latest peak of negative S (active deformation) recorded in the basal or midsegments of the lateral and septal walls in the 4-chamber apical view (TMinMax). S (deformation) was preferred to velocity assessment because of the new 2D-S abilities and because of the theoretic advantage of S over velocity assessment. A simplification of the DYS index initially described by Yu et al.13 for the velocity assessment was used as reported by Poerner et al.19 For each myocardial segment, we initially measured the time interval from the onset of the QRS complex to the peak value of S within the heart cycle analyzed.

Statistical Analyses

The reproducibility of the DTI and 2D-STS measurements was examined by reanalyzing the data of randomly selected patients for intraobserver (n = 15) and interobserver (n = 15) variability. The absolute difference (variability) was defined as observer 1−observer 2 and the relative difference as observer 1−observer 2 divided by the averaged measurements of observer 1 and observer 2 for each patient. Continuous variables are presented as means ± SD. The measurements of longitudinal S (DTI-S and 2D-STS) were compared using a linear regression analysis, combined with Bland and Altman plots showing the mean difference and 95% confidence interval. The correlation between DTI and 2D-STS on the one hand, and QRS duration on the other, was examined using the Pearson R coefficient calculation completed by a univariate linear regression analysis. The baseline characteristics of the ischemic versus nonischemic groups were compared by paired Student t test. Statistical analyses were performed using statistical software (SPSS, Version 10.0, SPSS Inc, Chicago, IL). A P value less than .05 was considered statistically significant.
Pulse Doppler echocardiogram. The variability in the measurements QRS onset and the onset of pulmonary or aortic flow recorded on between measurements was 3.8% for the time interval between the QRS duration in the NICM group versus 29.8 ± 25.4 milliseconds in the ICM group (P < .003). The difference between the two groups was highly significant (P < .003). A correlation was observed between QRS width and interventricular DYS (Q-aortic – Q-Ap) in patients with NICM (r = 0.42, P = .003), but not in the ICM group.

Interventricular DYS

Pulsed Doppler Q-aortic valve and Q-pulmonary valve opening. Mean ± SD values are displayed in Table 3. Interventricular DYS was 40.2 ± 29.6 milliseconds in the NICM group versus 29.8 ± 25.4 milliseconds in the ICM group (P = .03). A correlation was observed between QRS width and interventricular DYS (Q-aortic – Q-Ap) in patients with NICM (r = 0.42, P = .003), but not in the ICM group.

Longitudinal function assessed by DTI. In patients with NICM, the asynchrony index calculated from DTI-S time to peaks was correlated with the QRS duration (r = 0.47, P = .001) and with the time delay Q-aortic valve opening (r = 0.34, P = .01). Similar correlations were not found in the subgroup of patients with ICM.

Longitudinal function assessed by 2D-S. In the longitudinal direction, a correlation was observed between the asymptynchrony index calculated from the 2D-STS time to peaks and QRS duration in patients with HF and nonischemic heart disease (r = 0.43, P = .003). This correlation was not present in patients with ischemic heart disease (Figures 3 and 4).

Radial function assessed by 2D-S. In the radial direction, the asynchrony index calculated from 2D-STS time to peaks was correlated with the QRS duration in patients with NICM (r = 0.43, P = .003) and patients with ICM (r = 0.48, P = .003) (Figures 3, 4, and 5). It did not correlate with Q-aortic time delay.

Table 1 Baseline characteristics of patients with nonischemic versus ischemic cardiomyopathies

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 12)</th>
<th>NICM (n = 49)</th>
<th>ICM (n = 46)</th>
<th>P</th>
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<tr>
<td>Age, y</td>
<td>52 ± 14.9</td>
<td>60.1 ± 12.8</td>
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<td>Male, No</td>
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<td>44</td>
<td>39</td>
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<td>Weight, kg</td>
<td>68.8 ± 11.6</td>
<td>72.7 ± 18.1</td>
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<tr>
<td>Height, cm</td>
<td>168.8 ± 8.3</td>
<td>169.7 ± 25.5</td>
<td>169.6 ± 35.6</td>
<td>.5</td>
</tr>
<tr>
<td>New York Heart Association functional class</td>
<td>1</td>
<td>2.3 ± 1.1</td>
<td>2.8 ± 1.2</td>
<td>.03</td>
</tr>
<tr>
<td>Peak oxygen consumption, mL/kg</td>
<td>Not done</td>
<td>17.5 ± 9.8</td>
<td>18.0 ± 9.1</td>
<td>.4</td>
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<tr>
<td>Left ventricular ejection fraction, %</td>
<td>61 ± 6.5</td>
<td>27.3 ± 7.5</td>
<td>24.8 ± 7.9</td>
<td>.24</td>
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<td>QRS duration, ms</td>
<td>82.6 ± 12.5</td>
<td>132.9 ± 36.2</td>
<td>134.7 ± 45.1</td>
<td>.87</td>
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</tbody>
</table>

ICM, Ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; ns, not significant.

Values are means ± SD.

The P value concerns the t test between the two cardiomyopathy groups.

RESULTS

Study Groups
Between May and September 2005, 95 consecutive patients presenting with chronic systolic HF (LV EF ≤40%, and LV end-diastolic diameter ≥55 mm) were included in this study. The underlying heart disease was ischemic cardiomyopathy (ICM) in 46 patients non-ICM (NICM) in 49 patients. The baseline characteristics of the two study groups are presented in Table 1, as are the characteristics of the control population.

Mean LV EF and QRS duration were similar in both groups. All patients were optimally medically treated according to their NYHA HF functional class.1,2

Reliability of Tissue Doppler and 2D-STS Measurements
We first compared the results of the assessment of mechanical DYS using LV myocardial deformation. This was possible in the longitudinal direction only, because DTI does not allow a calculation of myocardial deformation in the radial direction based on the apical view. A correlation was observed for the entire population (R = 0.6, P < .001) and in both study subgroups (Figures 1 and 2).

Reproducibility of Measurements
The intraobserver and interobserver reproducibility of the measurements tested, for 15 patients, is shown in Table 2. The variability between measurements was 3.8% for the time interval between the QRS onset and the onset of pulmonary or aortic flow recorded on pulse Doppler echocardiogram. The variability in the measurements of time intervals between QRS onset and peak of regional S on DTI or 2D-STS ranged between 5.8% and 11.6%.

The reproducibility for the peak values was better in 2D-S than in DTI (variation coefficient: 8.5% and 9.8% for the intraobserver and the interobservers variability, respectively) considering the longitudinal function assessment. In regard to the radial (or transversal) function assessment from the apical window, the coefficients of variation were 20.3% and 18.6%, respectively, for the intraobserver and the interobserver variability using the 2D-STS radial (Table 2).

Interventricular DYS

Pulsed Doppler Q-aortic valve and Q-pulmonary valve opening. Mean ± SD values are displayed in Table 3. Interventricular DYS was 40.2 ± 29.6 milliseconds in the NICM group versus 29.8 ± 25.4 milliseconds in the ICM group (P = .03). A correlation was observed between QRS width and interventricular DYS (Q-aortic – Q-Ap) in patients with NICM (r = 0.42, P = .003), but not in the ICM group.

Interventricular DYS

Pulsed Doppler QRS onset to aortic outflow time delay. Q-aortic was 148.8 ± 38.2 milliseconds in the NICM group versus 130.9 ± 38.05 milliseconds in the ICM group (Table 3). The difference between the two groups was highly significant (P < .008). The Q-aortic time delay was, however, correlated with QRS duration in both study subgroups (r = 0.44, P = .001 in NICM, and r = 0.4, P = .006 in ICM).

Longitudinal function assessed by DTI. In patients with NICM, the asynchrony index calculated from DTI-S time to peaks was correlated with the QRS duration (r = 0.47, P = .001) and with the time delay Q-aortic valve opening (r = 0.34, P = .01). Similar correlations were not found in the subgroup of patients with ICM (Figures 3, 4, and 5).

Longitudinal function assessed by 2D-S. In the longitudinal direction, a correlation was observed between the asynchrony index calculated from the 2D-STS time to peaks and QRS duration in patients with HF and nonischemic heart disease (r = 0.43, P = .003). This correlation was not present in patients with ischemic heart disease (Figures 3 and 4).

Radial function assessed by 2D-S. In the radial direction, the asynchrony index calculated from 2D-STS time to peaks was correlated with the QRS duration in patients with NICM (r = 0.43, P = .003) and patients with ICM (r = 0.48, P = .003) (Figures 3, 4, and 5). It did not correlate with Q-aortic time delay.
Mechanical DYS parameters according to the QRS duration.

As many patients of the series analyzed had QRS less than 120 milliseconds, a dedicated comparison of patient having a QRS of 120 milliseconds or less versus QRS greater than 120 milliseconds is displayed in Table 4. The larger the QRS the more abnormal the parameters of interventricular and intraventricular mechanical DYS were: aortic pre-ejection time was significantly longer in patient with large QRS (127 ± 34.7 vs 151.9 ± 40.4 milliseconds, P < .001). Interventricular time delays were also significantly larger, as were DYS indices in the longitudinal and the radial direction.

DISCUSSION

This study showed that ventricular DYS can be assessed by analyzing longitudinal and radial 2D-STS from a single apical view. This new means of myocardial mechanical properties quantification is very promising. Different profiles of DYS were found, which were influenced by the underlying cause of HF. ICM and NICM appeared to have different myocardial contractile behaviors that resulted in different electromechanical correlates.

Arguments for Mechanical DYS Assessment

Recent work has demonstrated that intraventricular DYS is a common finding in patients with systolic HF. But our initial interest in measuring mechanical DYS was guided by the fact that, using electrical criterion, up to 30% of recipients of CRT system do not respond to the therapy. An assessment of mechanical inter- and intra-LV DYS has, therefore, been suggested in addition to electrical DYS. Delays between opposite LV walls greater than 65 milliseconds in the longitudinal, and greater than 130 milliseconds in the radial, direction have been proposed. Weak correlation between electrical and mechanical DYS have been reported. Our approach was to assess electric and mechanical correlation not in patients corresponding to current guidelines for CRT, but in a chronic stable systolic HF population. We observed also weak correlations between QRS duration and echocardiogram.
Actually, a correlation might exist in some patients and not in others. In our series, patients with larger QRS durations were also the one having the most pathologic indices of mechanical DYS. This was found whatever the cause of the underlying cardiomyopathy. It depends on the capability of the dyssynchronized myocardial segments to impact on the vectorial sum of electrical forces represented by the QRS duration. The degree of fibrosis, the type of remodeling, and the underlying cause of the cardiomyopathy impact on these correlations between electrical and mechanical DYS as we observed comparing patients with ischemic and nonischemic conditions. So, until now, the beneficial effect of CRT has been demonstrated based on the electrocardiogram. However, electrocardiography is potentially insufficient, especially for partly ischemic or fibrotic myocardium. The observation of mechanical DYS in patients with narrow QRS and the fact that CRT has been successfully applied in these very few and selected patients despite QRS duration less than 120 milliseconds provides a demonstrative example of this occasional absence of correlation between electrical and mechanical DYS.

Complexity of LV Myocardial Mechanical Characteristics, Importance of the Underlying Myocardial Disease: Relevance of the 2D-S Capabilities

The architecture and contractile function of the LV are complex. In the subendocardium, the myocardial fibers are oriented in an approximately longitudinal direction, whereas in the midmyocardium they are oriented in a circumferential (radial) direction, and in the subepicardium they are oriented obliquely. Differences in timing of contraction exist not only between segments and walls, but also between longitudinal and radial shortening within the same segment. For the assessment of regional myocardial function and DYS, ultrasound imaging of tissue deformation has been shown to be
clinically useful. DTI allows only the measurement of 1-dimensional S, and in a limited number of myocardial segments and directions. Thus, after comparing its result to DTI-S, we applied, in an apical window, the recent 2D-STS, enabling the calculation of tissue deformation by tracking unique 2D speckles within the image in two orthogonal planes. No angle dependency and an approximately 15-millisecond temporal resolution but a relatively weak reproducibility in radial direction are characterizing 2D-STS. Longitudinal 2D-STS was correlated with a 10% or less interobserver variability to DTI-S in the apical 4-chamber view. The curves obtained with 2D-STS were smoother. The peak of deformation values (percent) obtained with 2D-STS were slightly lower than with DTI-S. On the other hand, this frame rate limitation did not interfere with the assessment of DYS (timing), as observed by Suffoletto et al using the parasternal short-axis view. Our experience, in patients with chronic HF, was, however, that image quality was better using apical windows than parasternal ones. This new possibilities offered by 2D-STS appears, thus, extremely relevant because myocardial contractility is nonisotropic and because the sensitivity to DYS varies among the 3 components of LV myocardial function.
that electrical and mechanical DYS correlated homogeneously in patients with NICM (considering radial and longitudinal LV regional deformation) in contrast to what was observed in ICM. In ICM, radial DYS was the best mechanical index that correlated with QRS duration. Assessment of radial, instead of longitudinal, DYS only might be, in ICM especially, relevant and perhaps appropriate to select candidates for CRT.\textsuperscript{16,33} So, as we tested, 2D-S new facilities will probably be useful in patient selection for CRT. It can be furthermore integrated to the viability testing sometimes proposed for ICM, to predict improvement of LV performance after CRT\textsuperscript{34,35}

Limitations

2D-STS might be a suitable method for the routine assessment of mechanical DYS. However, care must be taken to acquire images with the highest gray-scale definition, using a frame rate of approximately 70 Hz, including the endocardial and epicardial interfaces. In addition, the endocardial border tracing must be manually optimized. Thus, further prospective multicenter studies are warranted to confirm the clinical contributions of this new and promising imaging method. We proposed the use of the 2D-S taking into account that there is no gold standard at this stage despite a large number of methods proposed.

Electrical and mechanical DYS assessed by regional S are different, the latter being influenced by the former, although not exclusively. The reproducibility of measurements was sometimes moderate, illustrating the difficulties encountered with a single echocardiographic method of assessment of DYS. The use of multiple methods, instead of a single technique and parameter, might be preferable when assessing DYS in clinical practice.

Conclusions

We have shown that radial and longitudinal DYS can be assessed by 2D-STS within a single cardiac cycle and in the same region of interest. The correlation between electrical and mechanical indices in patients with ICM versus NICM was dissimilar, illustrating the importance of the assessment of mechanical DYS. In a variety of clinical situations, the study of longitudinal DYS might be easier and, in patients with dilated NICM, diagnostically helpful, although it is less sensitive than radial DYS. This radial DYS assessment relevance compared with longitudinal DYS ones warrants further investigations, particularly in complex heart disease, as in most cases of chronic ICM.

Table 4 Measurements of interventricular and intraventricular asynchrony in nonischemic and ischemic cardiomyopathies according to QRS duration

<table>
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<tr>
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<th>QRS &gt; 120 ms (n = 51)</th>
<th>P value</th>
</tr>
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<tr>
<td>Interventricular dyssynchrony, ms</td>
<td>25.9 ± 22.3</td>
<td>43.4 ± 30.4</td>
<td>.001</td>
</tr>
<tr>
<td>NICM</td>
<td>26.1 ± 23.7</td>
<td>51.1 ± 30.4</td>
<td>.001</td>
</tr>
<tr>
<td>ICM</td>
<td>25.7 ± 21.3</td>
<td>33.5 ± 27.1</td>
<td>.04</td>
</tr>
<tr>
<td>Pre-ejection time, ms</td>
<td>127.0 ± 34.7</td>
<td>151.9 ± 40.4</td>
<td>.0003</td>
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<td>Aortic</td>
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<td>160.8 ± 34.7</td>
<td>.0001</td>
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<td>NICM</td>
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<td>Pulmonary</td>
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<td>Intraventricular dyssynchrony, ms</td>
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<td>Longitudinal 2D-STS</td>
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<td>ICM</td>
<td>51.4 ± 41.7</td>
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</table>

DTI, Doppler tissue imaging; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; STS, speckle-tracking strain; 2D, two-dimensional. Values are means ± SD.

REFERENCES


