Impact of Loading Condition on the 2D Speckle Tracking–Derived Left Ventricular Dyssynchrony Index in Nonischemic Dilated Cardiomyopathy

Hyo Eun Park, MD; Sung-A Chang, MD, PhD; Hyung-Kwan Kim, MD, PhD; Dong-Ho Shin, MD, MPH; Ji-Hyun Kim, MD; Myung-Ki Seo, MD; Yong-Jin Kim, MD, PhD; Goo-Yeong Cho, MD, PhD; Dae-Won Sohn, MD, PhD; Byung-Hee Oh, MD, PhD; Young-Bae Park, MD, PhD

Background—The effects of left ventricular (LV) loading conditions on LV dyssynchrony have not been elucidated. We modified LV loading conditions to reveal their effects on echocardiography-derived LV dyssynchrony index (LVdys) in patients with documented nonischemic dilated cardiomyopathy.

Methods and Results—Thirty-seven patients were consecutively enrolled. After baseline measurements, pneumatic compression of the lower extremities (Pcom) was used to increase LV afterload. Subsequently, sublingual nitroglycerin (SL-NG) was administered to modify preload. Conventional echocardiographic parameters, LVdys (by speckle-tracking radial strain analysis) and LV end-systolic wall stress (LV-ESWS), were calculated under each condition. LVdys-6 (defined as the maximal difference in time-to-peak radial strain between 6 myocardial segments) and LV-ESWS increased under Pcom (for LVdys-6, 159±117 at baseline versus 239±140 ms under Pcom, P<0.05; for LV-ESWS, 191±63 versus 228±80 g/m², P<0.05) After SL-NG application, both parameters decreased significantly (for LVdys-6, 239±140 under Pcom versus 147±103 ms after SL-NG, P<0.05; for LV-ESWS, 228±80 under Pcom versus 189±67 g/m² after SL-NG, P<0.05). When the presence of LV dyssynchrony was defined as the absolute difference in time-to-peak radial strain between the anteroseptal and posterior segments (LVdys-2), the results were unchanged. Using 130 ms as a cutoff value, the proportion of patients with LV dyssynchrony changed significantly (29.7% at baseline, 45.9% under Pcom, and 35.1% after SL-NG). When the presence of LV dyssynchrony was defined as standard deviation of the time to peak radial strain for 6 segments (LVdys-SD), the results were same. LVdys and LV-ESWS showed a modest but significant association with each other (r=0.47, P<0.001 for LVdys-6; r=0.41, P<0.001 for LVdys-2; r=0.46, P<0.001 for LVdys-SD).

Conclusions—To the best of our knowledge, the present study provides the first evidence of a significant association between LVdys and LV loading status, reflective of a dynamic nature of LVdys. Accordingly, LV loading conditions should be taken into account when echocardiographic LVdys is used for clinical decision-making of selecting candidates for cardiac resynchronization therapy or when it is used as a surrogate marker of prognosis. (Circ Cardiovasc Imaging, 2010;3:272-281.)

Key Words: left ventricle ■ dyssynchrony ■ echocardiography ■ speckle tracking ■ hemodynamics

Left ventricular (LV) dyssynchronous movement is not uncommon in patients with nonischemic dilated cardiomyopathy (DCM) and is known to be closely associated with impairment of LV systolic function and a poor long-term prognosis.1–3 Restoring synchronicity of LV contraction by cardiac resynchronization therapy (CRT) has shown improvement in quality of life, functional status, morbidity, and mortality in patients with drug-refractory heart failure.4–6 However, 30% of patients did not respond to this sophisticated treatment,4,6 which underlines the need for better selection criteria. To meet this requirement, continued attempts have been made to identify CRT responders more effectively before device implantation by using a variety of echocardiographic LV dyssynchrony indexes (LVdys).7–14

Received June 30, 2009; accepted February 19, 2010.

From the Division of Cardiology (H.E.P., H.-K.K., D.-H.S., J.-H.K., M.K.S., Y.-J.K., G.-Y.C., D.-W.S., B.-H.O., Y.-B.P.), Department of Internal Medicine, Cardiovascular Center, Seoul National University Hospital; and the Division of Cardiology (S.-A.C.), Department of Internal Medicine, Cardiac and Vascular Center, Samsung Medical Center, Seoul, Korea.

This study was not registered as a clinical trial because patient enrollment began before July 1, 2008. In addition, interventions in this study were used as a simple tool to reveal the dependence of LV dyssynchrony index on LV loading condition. Thus, this study did not directly relate interventions (pneumatic compression or sublingual nitroglycerin) to health outcomes (patients’ prognosis).

Correspondence to Hyung-Kwan Kim, MD, PhD, Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul, 110-744, Korea. E-mail cardiman@medimail.co.kr or hkkim73@snu.ac.kr

© 2010 American Heart Association, Inc.

Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.109.890848
Despite encouraging preliminary data, LV dys derived from standard M-mode or tissue velocity imaging (TVI) techniques showed disappointing results with respect to prediction of CRT responders in the PROSPECT trial, in which sensitivity and specificity for the prediction of beneficial CRT response were only modest with low yields and high variability for dyssynchrony measurements. Discrepancies between the findings of the PROSPECT trial and previous studies can be partially explained by recent work showing that longitudinal cardiac rotation may modify the profile and amplitude of systolic myocardial velocity, giving the impression that LV dys measurement by the TVI technique is inaccurate or irreproducible. In addition to this limitation, TVI is susceptible to angle dependency, the tethering effect, or translational motion of the myocardium, which inhibits its widespread clinical applicability.

Clinical Perspective on p 281

Speckle-tracking echocardiography (STE) is a novel method used to quantify regional strain from routine B-mode gray-scale images. Unlike TVI, STE-derived radial strain has advantages in terms of LV dys measurement, thanks to its angle independency and its freedom of tethering and translational effects. Although no echocardiographic parameters have proven ideal for assessment of CRT responders, STE may have certain technical advantages. Heart failure is considered a dynamic condition because LV loading status can be changed by a variety of medications used to reduce patient symptoms. For example, vasodilators such as nitrates, which are frequently used to reduce LV preload, can significantly affect LV volume and thus loading status. Although STE-derived radial strain can circumvent the inherent limitations of TVI, the potential impact of physiological state of individual patients on LV dys should be unraveled before STE-determined LV dys is adopted in a multicenter clinical trial (such as PROSPECT) and is used clinically. This issue is also clinically important, given recent efforts to use LV dys as a surrogate marker of prognosis in a variety of populations. However, to date, there is a paucity of data concerning the potential influence of changes in LV loading condition on LV dys.

Therefore, we sought to investigate the effect of LV loading conditions on LV dys measurement in patients with nonischemic dilated cardiomyopathy using STE-derived radial strain analysis.

Methods

Study Population

Forty-seven consecutive patients who were diagnosed as having nonischemic DCMP were initially considered for this study. All patients had undergone coronary angiography and were confirmed to be free of significant coronary artery disease (defined as luminal stenosis of >50% in any epicardial coronary artery). All patients initially recruited were in sinus rhythm on 12-lead ECG and were free of any congenital heart disease, valvular heart disease, or arrhythmias. Among them, 10 patients were excluded from the analyses because of poor echocardiographic image quality (5 patients), poor speckle tracking (2 patients), or an LV ejection fraction of ≥40% by the modified biplane Simpson method (3 patients). Finally, 37 patients were left in the final analyses, who are the subjects of the current study. All patients were fully informed about the procedure, and written informed consent was obtained from all participants before enrollment. The study protocol was approved by the institutional review board of our hospital.

Sample Size Calculation

The number of the study population was calculated based on the previous experiences, because, hitherto, we could not find any study similar to ours. We estimated study sample size in the assumption of α-error of 0.05 and β-error of 0.20, with a statistical power of 80%. We assumed that around 100 ms, change in the LV dys-6 can be found with a standard deviation of LV dys-6 of 80 ms. Because we must measure LV dysynchrony under 3 different loading conditions for each patient, a total of 33 patients should be enrolled. When we supposed that 10% of patients should be excluded possibly because of difficulty in the application of the speckle-tracking technique, the number of patients that should be recruited is about 35 for the present study.

Study Protocol

Baseline transthoracic echocardiograms were obtained using commercially available equipment (Vivid 7, GE Medical Systems, Milwaukee, Wis) in a left lateral decubitus position. During routine echocardiographic examinations, we determined the appropriateness of the patients for inclusion on the basis of 2D echocardiographic image quality. Patients with technically inappropriate image quality were excluded at this stage.

Blood pressure (BP) and heart rate (HR) were measured initially after a 20-minute resting period. Routine standard echocardiographic examinations included measurements of LV end-diastolic wall thicknesses, LV end-diastolic and end-systolic volumes, and LV ejection fraction (LVEF) using the modified biplane Simpson method, pulsed-wave Doppler examination of the mitral inflow, and pulsed-wave tissue Doppler imaging at the medial mitral annulus. From the mitral inflow Doppler signals, early transmirtal inflow velocity (E), late transmirtal inflow velocity (A), and deceleration time (DT) of E velocity were obtained with the sample volume placed between the tips of mitral leaflets. Standard M-mode and 2D images were obtained during end-expiratory breath-hold for better image acquisition and stored in cine loop format from 3 consecutive beats. After acquisition of the baseline transthoracic echocardiographic images, pneumatic trousers without the bladder for compression of the lower abdomen were put on the patients (Figure 1A and 1B). At the beginning of the study, a specially designed compressor inflated the pneumatic trousers to 100 mm Hg of pressure on both lower extremities and inflation was maintained throughout the examination. Echocardiographic images for STE-derived LV dys began to be scanned 3 minutes after pulmonary compression of the lower extremities (Pcm). The BP and HR were again measured under Pcm. After finishing procurement of echocardiographic images under Pcm, pneumatic trousers were deflated and removed, and 1 tablet (0.6 mg) of sublingual nitroglycerine (SL-NG) was given to the patient. The target BP was set at least at the baseline value 3 minutes after SL-NG. In the case of high BP even after 1 tablet (0.6 mg) of SL-NG, another NG tablet was administered to the patient sublingually. After confirming achievement of target BP, acquisition of echocardiographic images was commenced. SL-NG could not be administered in 1 patient with low BP, in whom baseline systolic BP was only 90 mm Hg.

Because systemic vascular resistance was reported to be an unreliable index of LV afterload, we calculated LV end-systolic wall stress (LV-ESWS) as a reliable representative of LV afterload, in an attempt to quantify the cardiac effect of either Pcm or SL-NG administration. LV-ESWS was calculated using the following formula:

\[
\text{LV end-systolic wall stress} = \left( \frac{\text{Des}}{\text{Hes}} \right) (1 + \frac{\text{Hes}}{\text{Des}}) (0.34),
\]

where LV end-systolic wall stress is in g/cm², Pes, which stands for LV end-systolic pressure, is in mm Hg. Des and Hes are in LV end-systolic dimension and wall thickness in cm, and 0.34 is the...
factor for converting Pes from mm Hg to g/cm². Because there were no subjects with aortic stenosis, Pes could be replaced with the noninvasively determined systolic BP. To evaluate the dependency of QRS duration on LV loading status, ECG was also obtained in randomly selected 13 patients under 3 different loading conditions.

STE Assessments
After standard echocardiographic examinations, we scanned and recorded the parasternal short-axis at the level of papillary muscles using a M3S probe without a dual-focusing tool. Frame rate (range, 80–100 frames/s) and probe frequency (range, 1.7–2.0 MHz) were adjusted during end-expiratory breath-hold for optimal image acquisition. Sector width and image depth were optimized to maintain an adequate frame rate without losing the 2D image quality. STE-derived radial strain was assessed on LV short-axis images at the papillary muscle level. Special care was taken not to get oblique LV short-axis images and to obtain short-axis images with the most circular geometry possible. Three consecutive heart beats were digitally stored in cineloop format and were analyzed offline. Image analysis was performed by 1 independent cardiologist who was blinded to the status of the image acquisition, using a customized dedicated software package (EchoPac 5.0.1 for PC, GE Medical Systems, Horten, Norway).

From an end-systolic single frame, a region of interest was manually defined on the endocardial cavity interface by a point-and-click approach. An automated tracking system then followed the endocardium throughout the cardiac cycle. The validity of tracking was verified by reliability parameter offered by system (V indicates valid tracking, X, unacceptable tracking) and was again visually checked. Further adjustment of the region of interest was performed to ensure that all of the myocardial regions were included as needed. The traced endocardium was automatically divided into 6 standard segments: inferoseptal, anteroseptal, anterior, anterolateral, posterior, and inferior. Finally, time–radial strain curves for all the 6 myocardial segments were automatically constructed, where time from QRS onset to peak radial strain was obtained. As a consequence, the segments showing the earliest and latest peak radial strain and the heterogeneity in time-to-peak radial strain for the 6 myocardial segments were determined. In the current study, LVdys was defined in 3 different ways: (1) the maximal time delay measured between the first and last segments to reach the peak radial strain (LVdys-6), (2) the absolute time difference in time-to-peak radial strain for the anteroseptal versus posterior segment (LVdys-2), in which a time interval of ≥130 ms was accepted for the presence of LV dyssynchrony, and (3) standard deviation of the time to peak radial strain for 6 myocardial segments (LVdys-SD).

Statistical Analysis
Data are expressed as mean±SD for continuous variables and as frequencies and percentages for categorical variables. The Friedman test was performed to compare continuous variables under 3 different loading conditions simultaneously. The Wilcoxon signed-rank test was performed for pairwise comparisons of continuous variables obtained under different loading conditions. Because of the possibility of an inflation of type I error that is derived from multiple comparisons, a probability value of <0.017 was adopted for statistical significance in this particular analysis. In the remaining statistical analyses, a probability value of <0.05 was considered statistically significant. Spearman correlation analysis was used to compare relationships between continuous variables. All statistical analyses were performed with statistical software package (SPSS 13.0, SPSS Inc, Chicago, Ill.).

Results
Table 1 summarizes the baseline clinical and conventional echocardiographic characteristics of the 37 patients.

Feasibility of STE-Derived Radial Strain Analysis
A total of 660 segments (222 segments at baseline and under Pcom and 216 segments after SL-NG) were analyzed for STE-derived radial strain. Of these 660 segments, 11 were excluded because of poor speckle tracking even after manual adjustment of the endocardial border delineation. Finally, the first and last mechanical activations to peak radial strain throughout cardiac cycle were investigated in 649 of the segments (98.3%).

Changes in Clinical and Conventional Echocardiographic Parameters
Changes in clinical and conventional echocardiographic variables and in LV-ESWS are illustrated under different loading conditions in Table 2. As expected, Pcom led to a significant rise in systolic BP, diastolic BP, and LV-ESWS, but HR remained unchanged. Results after SL-NG administration were in contrast to those after Pcom; that is, there was a significant decrease in SBP, DBP, and LV-ESWS, but no significant change in HR was observed as compared with those under Pcom. A change in LV-ESWS according to loading conditions is illustrated in Figure 2. QRS duration obtained in 13 patients did not change according to loading status.

LVdys Based on Maximal Difference Among 6 Segments (LVdys-6)
Modification of LV loading conditions by Pcom or SL-NG exerted a significant effect on LVdys-6 (Table 2
Table 1. Baseline Clinical and Echocardiographic Characteristics of the 37 Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>n=37</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56 ± 15</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>23 (62%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.4 ± 3.0</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>124 ± 19</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>74 ± 13</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75 ± 16</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (41%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>27 (73%)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>22 (60%)</td>
</tr>
<tr>
<td>CCBs</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>24 (65%)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11 (24.3%)</td>
</tr>
<tr>
<td>III</td>
<td>26 (75.7%)</td>
</tr>
<tr>
<td>Type of rhythm</td>
<td></td>
</tr>
<tr>
<td>LBBB, n (%)</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>131 ± 40</td>
</tr>
<tr>
<td><strong>Conventional echocardiographic variables</strong></td>
<td></td>
</tr>
<tr>
<td>LVIDs, mm</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>LVd, mm</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>LVPWd, mm</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>LV-EDV, mL</td>
<td>222.7 ± 57.9</td>
</tr>
<tr>
<td>LV-ESV, mL</td>
<td>158.1 ± 50.7</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>29.6 ± 7.2</td>
</tr>
<tr>
<td>Left atrial size, mm</td>
<td>46.8 ± 6.7</td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>A, m/s</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>DT, ms</td>
<td>169 ± 62</td>
</tr>
<tr>
<td>E′, m/s</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>S′, m/s</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure, mm Hg</td>
<td>37 ± 12</td>
</tr>
<tr>
<td>LV-ESWS, g/cm²</td>
<td>190.9 ± 62.5</td>
</tr>
<tr>
<td>Frame rate</td>
<td>90 ± 15</td>
</tr>
<tr>
<td>LVdys-6, ms</td>
<td>159 ± 117</td>
</tr>
<tr>
<td>LVdys-2, ms</td>
<td>118.3 ± 107.7</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP and DBP, systolic and diastolic blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCBs, calcium-channel blockers; LBBB, left bundle-branch block; LVIDs and LVd, left ventricular end-systolic and end-diastolic dimension; LVPWd, LV end-diastolic posterior wall thickness; LV-EDV and LV-ESV, LV end-diastolic and end-systolic volume; and LV-ESWS, LV end-systolic wall stress.

*By biplane modified Simpson method.

Table 2. Comparison of Clinical and Echocardiographic Parameters Under Different Loading Conditions

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline (n=37)</th>
<th>Pneumatic Compression (n=37)</th>
<th>SL-NG (n=36)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>75 ± 16</td>
<td>74 ± 16</td>
<td>77 ± 16</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124 ± 19</td>
<td>130 ± 21*</td>
<td>114 ± 18†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74 ± 13</td>
<td>76 ± 13</td>
<td>67 ± 10†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV-EDV, mL</td>
<td>222.7 ± 57.8</td>
<td>237.8 ± 55.2*</td>
<td>211.0 ± 61.6†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV-ESV, mL</td>
<td>158.1 ± 50.7</td>
<td>166.7 ± 49.4*</td>
<td>147.3 ± 55.9†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>29.6 ± 7.2</td>
<td>30.8 ± 6.5</td>
<td>31.6 ± 7.7</td>
<td>0.03</td>
</tr>
<tr>
<td>DT, ms</td>
<td>169 ± 62</td>
<td>156 ± 60</td>
<td>179 ± 74†</td>
<td>0.03</td>
</tr>
<tr>
<td>E/E′, ratio</td>
<td>21 ± 10</td>
<td>23 ± 10</td>
<td>17 ± 8†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS duration, ms, n=13</td>
<td>130 ± 37</td>
<td>136 ± 31</td>
<td>132 ± 27</td>
<td>0.21</td>
</tr>
<tr>
<td>LV-ESWS, g/cm²</td>
<td>190.9 ± 62.5</td>
<td>228.2 ± 80.0*</td>
<td>188.5 ± 66.7†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVdys-6, ms</td>
<td>158.6 ± 116.6</td>
<td>239.2 ± 140.1*</td>
<td>147.3 ± 103.1†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVdys-2, ms</td>
<td>118.3 ± 107.7</td>
<td>165.5 ± 122.8*</td>
<td>133.0 ± 115.1†</td>
<td>0.04</td>
</tr>
<tr>
<td>LVdys-SD</td>
<td>65.9 ± 49.9</td>
<td>98.8 ± 61.8*</td>
<td>66.7 ± 48.6†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LV-EDV and LV-ESV indicate LV end-diastolic and end-systolic volume; and LV-ESWS, LV end-systolic wall stress.

*P<0.017, baseline versus pneumatic compression.
†P<0.017, pneumatic compression versus SL-NG.
‡P<0.017, SL-NG versus baseline.
§By Friedman test.

from 239.2 ± 140.1 under Pcom to 147.3 ± 103.1 after SL-NG (P<0.001). A representative example of an STE-derived radial strain curve of a 51-year-old man who had an LVEF of 27%, QRS duration of 130 ms, and was

and Figure 3A). After Pcom application, radial strain curves revealed a significant increase in LVdys-6 from 158.6 ± 116.6 to 239.2 ± 140.1 (P<0.001), whereas SL-NG administration induced a significant decrease in LVdys-6

Figure 2. Change in LV-ESWS under different loading conditions.
of New York Heart Association class III is depicted in Figure 4.

LVdys Based on Time Delay Between Anteroseptal and Posterior Segments
Because a time delay ≥130 ms in the time-to-peak radial strain between the anteroseptal and posterior segments (ie, LVdys-2 ≥130 ms) has been reported to effectively predict CRT response, we again determined the presence of LV dyssynchrony using this cutoff value. At baseline, LV dysynchrony was present in only 11 patients (29.7%); however, the proportion of its presence was escalated up to 45.9% (17 patients) under Pcom. In turn, SL-NG administration decreased the proportion with an LVdys-2 of ≥130 ms to 35.1% (13 of 36 patients). Figure 5 illustrates the number of patients with an LVdys-2 of ≥130 ms under different loading conditions. As demonstrated in Figure 3B, as in LVdys-6 in Figure 3A, LVdys-2 was significantly dependent on LV loading conditions.

LVdys Based on Standard Deviation of the Time to Peak Radial Strain for 6 Segments
LVdys-SD increased significantly after Pcom application from 65.9±49.9 to 98.8±61.8 (P=0.002), whereas LVdys-SD showed a significant reduction from 98.8±61.8 under Pcom to 66.7±48.6 after SL-NG application (P=0.002) (Table 2 and Figure 3C).

Relationships Among LVdys-6, LVdys-2, or LVdys-SD and QRS Duration, LV Volumes, LVEF, and LV-ESWS
QRS duration on the 12-lead surface ECG displayed no significant correlation with LVdys-6 (r=0.31, P=0.053), LVdys-2 (r=0.31, P=0.056), or LVdys-SD (r=0.28, P=0.08). In contrast, LVdys-6, LVdys-2, and LVdys-SD all significantly increased in parallel with LV end-diastolic volume (r=0.48 for LVdys-6; r=0.38 for LVdys-2; r=0.48 for LVdys-SD, all P<0.001) and end-systolic volume (r=0.48 for LVdys-6; r=0.39 for LVdys-2; r=0.49 for LVdys-SD, all P<0.001), and E/E′ ratio (r=0.23, P=0.02 for LVdys-6; r=0.20, P=0.046 for LVdys-SD) when values obtained under different loading conditions were pooled. On the other hand, LVEF showed an inverse correlation with LVdys (r=−0.33, P=0.001 for LVdys-6; r=−0.30, P=0.002 for LVdys-2; r=−0.33, P<0.001 for LVdys-SD). With regard to LV-ESWS, there was a modest but significant positive correlation with LVdys-6, LVdys-2, and LVdys-SD (Figure 6A, 6B, and 6C).

Interobserver and Intraobserver Variabilities
Intraobserver variability was assessed using 2 different blinded evaluations by 1 observer for 60 segments in 10 randomly selected patients at least 30 days apart, whereas interobserver variability was assessed by 2 different observers at a different day. Interobserver and intraobserver variabilities for calculating STE-derived time-to-peak radial strain showed good agreements...
(intereobserver correlations: $r=0.97$, SEE=32 ms; intraobserver correlations: $r=0.96$, SEE=39 ms).

**Discussion**

In the present study, we found that the manipulation of LV loading conditions can produce a significant change in STE-derived LVdys. Of note, when 130 ms was used as a cutoff value for the presence of LV dyssynchrony, not a small proportion of patients, who did not have LV dyssynchrony at baseline, were reclassified as having LV dyssynchrony under Pcom. Likewise, SL-NG administration also significantly changed the proportion of patients who showed LV dyssynchrony. In particular, all LVdys exhibited a significant positive correlation with LV-ESWS, again advocating the dynamic nature of LVdys, depending on LV loading status.

**Necessity for Exploring the Impact of LV Loading Condition on LVdys**

CRT is currently regarded as an accepted therapeutic modality for patients with end-stage heart failure. A wide QRS complex on electrocardiograms, signifying electromechanical delay, has been considered a prerequisite for selecting patients who are likely to benefit from this sophisticated treatment. Nonetheless, about 30% of patients chosen using the current ECG-based selection criteria do not benefit from CRT. This is presumably because ECG-based QRS duration does not adequately reflect the presence of LV dyssynchrony. In this context, the ECG-based selection criteria are believed to be suboptimal for predicting a favorable response to CRT. The weight of current evidence favors the use of a mechanical LVdys measure with echocardiography as a superior method for predicting CRT response, in lieu of ECG-based LV dyssynchrony measure. However, the recent multicenter PROSPECT trial failed to prove an advantage of echocardiography-based LVdys (measured using the TVI or M-mode technique) over the current ECG-based criteria for predicting CRT response, which casts
doubt on the conceptual and theoretical merits of echocardiographically determined LVdys. Several reasons have been suggested for the unexpected results of the PROSPECT trial, such as inadequate patient selection, limitations of M-mode or TVI, and the lack of standardized data acquisition and analysis. We presumed that the physiological state of individual patients, for example, ventricular loading conditions, might be another contributor to the unexpected findings of the PROSPECT trial, on top of the limitations of echocardiographic methods used. The assumption on the possible contribution of ventricular loading conditions to LVdys is not entirely new, as indicated by a previous report; that is, the plasma levels of N-terminal pro-B-type natriuretic peptide showed large individual variances (median, 1920 pg/mL; interquartile range, 744–4288 pg/mL), implying that although all of the patients enrolled in the previous study met the current CRT indication, the severity of heart failure varied from patient to patient just before CRT implantation. A distinctive difference in the severity of heart failure as assessed using the plasma level of N-terminal pro-B-type natriuretic peptide as an objective marker could have been due in part to active medical treatments that modified LV preload or afterload; for example, vasodilators such as nitrates, which are frequently used to reduce LV preload, can affect LV volume or loading status.

A few reports previously showed that LV dyssynchrony can be changed during exercise. Lafitte et al reported that exercise can alter the extent of LV dyssynchrony, which also varied from patient to patient. The exercise-induced alteration in LVdys was observed in 26% of patients with heart failure and was associated with changes in cardiac output and severity of mitral regurgitation. However, our understanding of the possible relation between LV loading status and echocardiography-derived LVdys of the resting state (not exercise) is still lacking. Elucidation of this information is useful for effective clinical application of echocardiography-derived LVdys to the selection process of CRT candidates. In addition, given recent efforts made to use LVdys as a marker evaluating the effect of right ventricular pacing on LV function and to adopt LVdys to predict the effect of LV dyssynchrony on prognosis in various populations, potential association between LV loading status and echocardiography-derived LVdys assessed in the resting state should be established.

**Value of STE-Derived Radial Strain Analysis for Measuring LVdys**

Despite the wide use of TVI for LVdys measurement, it has several inherent limitations including vulnerability to the purported angle dependency, susceptibility to tethering or...
translational movements of myocardium, and an inability to discern between active contraction and passive movements of myocardium.29 Although strain rates derived from tissue Doppler velocities have theoretical merits and have been reported to be more accurate for predicting CRT response,29,30 they are highly susceptible to signal noise, and, as such, interobserver correlation is unsatisfactory.31 On the contrary, STE is a novel method based on routine gray-scale images, which permits the assessment of myocardial deformation in 2 dimensions with freedom from the directionality constraints of the Doppler method and enables actively contracting myocardial segments to be distinguished from those with passive movement.13,17,24,29 Furthermore, STE-derived strain measurements are semiautomatically performed with dedicated computer software, which significantly contributes to the high reproducibility of the values obtained.29 With these advantages, STE-derived strain analysis was recently proposed to be the best method to identify potential responders to CRT.17,32 Accordingly, on the basis of these theoretical and objective advantages, we used STE-derived radial strain analysis for LVdys assessment in the current study.

Impact of LV Loading Status on LVdys

Despite individual variations, we were able to demonstrate a dynamic change in LVdys in relation to instantaneous LV-ESWS; that is, the higher LV-ESWS, the greater LVdys. This relationship was consistently stable, irrespective of a sort of LVdys used according to the number of segments analyzed, that is, LVdys-6, LVdys-SD or LVdys-2. Moreover, we found a modest but statistically significant correlation between LVdys-6, LVdys-2 or LVdys-SD, and LV-ESWS, as shown in Figure 6A, 6B, and 6C. More importantly, dynamic changes in LVdys took place in the setting of a small change in LV-ESWS (from 190.9 g/cm² at baseline to 228.2 g/cm² under Pcom) without a demonstrable change in LV filling pressure, as evidenced by an insignificant rise in E/E’ ratio. Considering that release of B-type natriuretic peptide, another marker of LV filling pressure, is regulated primarily by changes in LV wall stress,33 the discrepancy between changes in LV filling pressure (as measured by E/E’ ratio) and LV-ESWS suggests that a change in LV-ESWS be regarded as an early phenomenon that occurs before an increase in LV filling pressure is clinically manifested. Given no change in E/E’ ratio before and after Pcom application, transient performance of Pcom does not appear to be enough to increase LV filling pressure; notwithstanding, LVdys displayed a significant alteration in parallel with a change in LV-ESWS, giving a hint that LVdys is a sensitive index and thus LVdys might be varied in a treatment-dependent manner, even in a patient. SL-NG administration leading to a reduction in both LV-ESWS and LV filling pressure also resulted in a significant drop in LVdys, which is another evidence of the dynamic nature of LVdys. In particular, with a time difference of 130 ms between the anteroseptal and posterior segments as a cutoff value for the presence of LV dyssynchrony, LV dyssynchrony was present in only 11 patients (29.7%); however, Pcom increased its presence up to 17 patients (45.9%). The subsequent administration of SL-NG markedly decreased the proportion of patients who showed the presence of LV dyssynchrony to 35.1% (13 of 36 patients). This observation is clinically important because there is a possibility that echocardiographic LVdys may be reported to be present one day but absent the next.

Taken together, the dependency of echocardiographic LVdys on LV loading status should be taken into account not only for evaluating CRT candidates but also in other studies that are designed to elucidate underlying mechanisms of specific diseases using echocardiographic LVdys23 or when LVdys is used as a surrogate marker for prognosis.3,18 Since the extent of LV dyssynchrony is affected by different LV loading conditions, we believe that achievement of medical optimization should be confirmed before assessing LV dyssynchrony with echocardiography to reduce false prediction of CRT response. In addition, exercise-related changes in LV dyssynchrony may be another aspect to be considered.28 Further works should be done to decipher enigma concerning the potential relation between echocardiographic LVdys during exercise and CRT response.

Study Limitations

Several limitations must be acknowledged. First, the number of patients recruited was relatively small. However, in an attempt to minimize potential bias caused by including a heterogeneous group of patients, we enrolled only patients with idiopathic DCMP, which allows for avoiding potential confounders likely to affect LVdys measurements. Thus, care should be taken when extrapolating our results to patients with ischemic cardiomyopathy. Second, we did not use conventional methods to modify LV loading status, for example, saline infusion. However, in patients with DCMP, it is unethical to infuse normal saline for study purposes without a definite clinical indication. To avoid ethical problems, we used Pcom as a safe maneuver for modification of LV loading status instead of saline infusion. The hemodynamic effects of Pcom include a significant increase in LV-ESWS, the most reliable surrogate measure for LV afterload,19 and in arterial BP without altering HR or cardiac output.34–36 The application of Pcom to DCMP patients appears to be safe because it has been used to treat patients in a shocked state.34,35 Moreover, with this device, we were able to determine that even a change in LV-ESWS that is insufficient to trigger a significant rise in LV filling pressure can lead to a significant increase in LVdys and thus cause a “false” classification of LV dyssynchrony status in a given patient. Finally, we are not in a position to propose an optimal timing for LVdys assessment in the prediction of CRT response, and thus additional studies are needed to determine the optimal patient status for assessing LVdys in a foreseeable future.

Conclusions

LVdys is significantly affected even by small extent of alteration of LV loading status and as such it should be considered a dynamic parameter. Therefore, LV loading conditions should be taken into account when echocardiographic LVdys is incorporated into future multicenter studies such as the PROSPECT trial, the selection process for CRT
candidates, or when LVDys is used as a surrogate marker of prognosis.

Sources of Funding
This study was supported in part by grants from the Korea Health 21 R&D Project, Ministry of Health and Welfare, South Korea (A090064), the Korea Liver Research Foundation, and the Handok Research Fund.

Disclosures
None.

References


CLINICAL PERSPECTIVE

Despite excellent results regarding use of cardiac resynchronization therapy, a treatment for restoring left ventricular (LV) synchronous contraction in patients with drug-refractory heart failure, approximately 30% of patients do not respond to this sophisticated treatment, underscoring the need for better selection criteria. Echocardiographic LV dyssynchrony index has recently been proposed as a better surrogate for predicting positive cardiac resynchronization therapy responders. Heart failure is considered a dynamic condition because LV loading status can be changed by a variety of medications used to improve patient symptoms. To date, however, there are few data concerning the potential influence of LV loading status on the echocardiographic assessment of LV dyssynchrony. We investigated the effect of LV loading condition on LV dyssynchrony in patients with nonischemic dilated cardiomyopathy using speckle-tracking–derived radial strain echocardiography. The measurement of LV dyssynchrony in this study (the maximal difference in time-to-peak radial strain in 2 or 6 segments as well as standard deviation of the time to peak radial strain for 6 segments) were significantly affected by changes in LV loading conditions created by sublingual nitroglycerin administration and pneumatic lower extremity compression. In particular, using 130 ms of difference between the anteroseptal and inferolateral segment as a cutoff value for the presence of LV dyssynchrony, the proportion of patients with LV dyssynchrony significantly changed (29.7% at baseline, 45.9% under pneumatic lower extremity compression, and 35.1% after sublingual nitroglycerin administration). Therefore, LV loading conditions should be considered when echocardiographic assessment of LV dyssynchrony is used for clinical decision-making.
Impact of Loading Condition on the 2D Speckle Tracking–Derived Left Ventricular Dyssynchrony Index in Nonischemic Dilated Cardiomyopathy

Hyo Eun Park, Sung-A Chang, Hyung-Kwan Kim, Dong-Ho Shin, Ji-Hyun Kim, Myung-Ki Seo, Yong-Jin Kim, Goo-Yeong Cho, Dae-Won Sohn, Byung-Hee Oh and Young-Bae Park

_Circ Cardiovasc Imaging_. 2010;3:272-281; originally published online February 27, 2010; doi: 10.1161/CIRCIMAGING.109.890848

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2010 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:

[http://circimaging.ahajournals.org/content/3/3/272](http://circimaging.ahajournals.org/content/3/3/272)