Left Ventricular Systolic Asynchrony is Induced Even in the Normal Heart During Increases in Afterload: A Study With Angiotensin II Stress Pulsed Tissue Doppler Imaging

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Abstract
Objective. We investigated whether pulsed tissue Doppler imaging could be useful to detect sensitively a decrease in left ventricular (LV) contractile force and development of systolic asynchrony during an increase in afterload in healthy individuals.

Methods. We recorded LV wall motion velocities before and after angiotensin II infusion by pulsed tissue Doppler imaging in 16 healthy individuals and evaluated the differences in the responses in systolic LV function along the short- and long-axes between the basal and apical regions during an acute increase in afterload.

Results. After angiotensin II infusion, the systolic blood pressure and LV end-systolic dimension were increased significantly, and the LV ejection fraction was significantly decreased. The peak first and second systolic velocities and the times from the beginning of the Q wave of the electrocardiogram to the peak first systolic velocity of the LV walls along both the short- and long-axes were markedly decreased and prolonged, respectively, in the apical region compared to the basal region.

Conclusion. LV systolic asynchrony is induced, even in normal hearts, during an increase in afterload. Pulsed tissue Doppler imaging provides incremental diagnostic information on regional LV systolic function.

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Key words: pulsed tissue Doppler imaging, afterload, left ventricular asynchrony

Introduction

Previous studies have reported that an increase in afterload is associated with a decrease in left ventricu-
ing, which facilitates the quantitative evaluation of regional LV myocardial function [6, 7].

**Methods**

**Study population**

We evaluated 16 healthy volunteers (10 men and 6 women, mean age 32 ± 10 years) in normal sinus rhythm without first-degree atrioventricular block. Each subject received an intravenous infusion of angiotensin II (Delivert; 0.01, 0.02, and 0.03 μg/kg/min infused at 10 minute intervals; Toa Eiyo, Tokyo, Japan) and saline solution to obtain a 30% increase in mean blood pressure [8]. Heart rate, systolic blood pressure (SBP), and M-mode echocardiographic and pulsed tissue Doppler imaging variables were measured during the infusion, and these variables were compared between baseline and after angiotensin II infusion.

The purpose of this study was fully explained to all subjects, and informed consent was obtained. The protocol was approved by the appropriate hospital committee regarding human experimentation.

**M-mode and 2-dimensional echocardiography**

Transthoracic M-mode echocardiograms were recorded with the use of a commercially available ultrasound diagnostic system (Power Vision 8000, Toshiba Corp, Tokyo, Japan) with a 2.5-MHz probe. The LV end-diastolic dimension (LVDd), end-systolic dimension (LVDs), maximum left atrial dimension, and end-diastolic thickness of the ventricular septum (VSth) and posterior wall (PWth) were determined. Using these parameters, we calculated the percent fractional shortening of the LV, as follows:

\[
\text{Percent fractional shortening of the LV (\%)} = \left( \frac{Dd-Ds}{Dd} \right) \times 100.
\]

LV end-diastolic and end-systolic volumes (EDV and ESV, respectively) were calculated from the apical 2- and 4-chamber views using a modified Simpson’s method. LV ejection fraction was calculated as EF = \( \frac{(EDV-ESV)/EDV} \times 100 \), where EF represents ejection fraction.

**Pulsed tissue Doppler imaging**

In the parasternal and apical long-axis LV echocardiograms, sample volumes were set in 4 subendocardial portions of the ventricular septum and posterior wall at the basal level including chordae tendineae and at the apical level excluding papillary muscles, respectively (Figure 1, top). The motion velocity patterns were recorded at the 4 sites along the short-axis from the parasternal long-axis view and at the 4 sites along the long-axis from the apical long-axis view by the pulsed Doppler method with a 3.75-MHz probe. Using the obtained patterns, the peak first and second systolic velocities (Sw1 and Sw2, respectively) and the time from the beginning of the Q wave of the electrocardiogram to the peak of the Sw1 (Q-Sw1) were determined (Figure 1, bottom).

Interobserver variability of measurements of the tis-

Fig. 1. Sample recording of motion velocity patterns of left ventricular wall by pulsed tissue Doppler imaging in parasternal (top, left) and apical (top, right) long-axis views and measurement of variables obtained from the motion velocity patterns of left ventricular wall. Sample volumes (open and closed circles) were set on subendocardial portions of ventricular septum (VS) and posterior wall (PW) at the basal level including chordae tendineae (open circles) and at the apical level excluding papillary muscles (closed circles). T, transducer; RV, right ventricle; LA, left atrium; Ao, ascending aorta; LV, left ventricle; Sw1 and Sw2, peak first and second systolic wall motion velocity, respectively; Q-Sw1, time from the beginning of the Q wave of the electrocardiogram to the peak Sw1; Ew, peak early diastolic wall motion velocity; Aw, peak atrial systolic wall motion velocity; ECG, electrocardiogram; PCG, phonocardiogram.
Doppler indices was calculated as the difference in 2 measurements in the same subject by 2 different observers divided by the mean value. Intraobserver variability also was calculated as the difference in 2 measurements in the same subject by 1 observer divided by the mean value.

**Statistical analysis**

Values are expressed as the mean ± SD. Changes in the heart rate, SBP, M-mode and 2-dimensional echocardiographic, and pulsed tissue Doppler imaging variables before and after angiotensin II infusion were compared by means of the 2-factor analysis of variance for repeated measurements. A P value < 0.05 was considered statistically significant.

**Results**

The clinical, M-mode and 2-dimensional, and pulsed tissue Doppler variables at baseline are summarized in Tables 1 and 2. No significant differences were found in heart rate (69 ± 10 vs. 67 ± 9 bpm), LVDd (4.3 ± 0.4 vs. 4.6 ± 0.5 cm), and maximum left atrial dimension (3.4 ± 0.4 vs. 3.5 ± 0.5 cm) before and after infusion of angiotensin II at 0.03 µg/kg/min. However, SBP and LVDd were significantly increased, whereas the percent fractional shortening of the LV and LV ejection fraction were significantly decreased after angiotensin II infusion (Figure 2).

The peak Sw1 and Sw2 of the ventricular septum and LV posterior wall along both the short- and long-axes were significantly decreased at the apical regions during angiotensin II administration at doses of 0.01 and 0.02 µg/kg/min (Figure 3). However, there were no significant changes in the mean peak Sw1 and Sw2 of the LV walls at the basal regions after infusion of angiotensin II at doses of 0.01 and 0.02 µg/kg/min. The Q-Sw1 was also significantly prolonged at the apical regions during angiotensin II administration at doses of 0.01 and 0.02 µg/kg/min compared to the basal regions (Figure 4). At a dose of 0.03 µg/kg/min of angiotensin II, changes in peak Sw1 and Sw2 and Q-

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**Table 1. Clinical, M-mode and 2-dimensional echocardiographic variables at baseline**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>SBP</th>
<th>LVDd</th>
<th>LVDs</th>
<th>%FS</th>
<th>EF</th>
<th>LAD</th>
<th>PWth</th>
<th>VSth</th>
</tr>
</thead>
<tbody>
<tr>
<td>(beats/min)</td>
<td></td>
<td>(mm Hg)</td>
<td>(cm)</td>
<td>(cm)</td>
<td>(%)</td>
<td>(%)</td>
<td>(cm)</td>
<td>(mm)</td>
<td>(mm)</td>
</tr>
<tr>
<td></td>
<td>69±10</td>
<td>118±15</td>
<td>4.3±0.4</td>
<td>2.5±0.4</td>
<td>40±6</td>
<td>62±5</td>
<td>3.4±0.4</td>
<td>10±2</td>
<td>11±3</td>
</tr>
</tbody>
</table>

HR, heart rate; SBP, systolic blood pressure; LVDd and LVDs, left ventricular end-diastolic and end-systolic dimension, respectively; %FS, percent fractional shortening of the left ventricle; EF, left ventricular ejection fraction; LAD, maximum left atrial dimension; PWth and VSth, end-diastolic thickness of the left ventricular posterior wall and ventricular septum, respectively.

**Table 2. Systolic pulsed tissue Doppler variables at baseline**

<table>
<thead>
<tr>
<th></th>
<th>Short-axis</th>
<th>Long-axis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sw1</td>
<td>Sw2</td>
</tr>
<tr>
<td></td>
<td>(cm/s)</td>
<td>(cm/s)</td>
</tr>
<tr>
<td>PW</td>
<td></td>
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</tr>
<tr>
<td>Basal</td>
<td>6.6±1.3</td>
<td>7.1±1.4</td>
</tr>
<tr>
<td>Apical</td>
<td>6.5±1.2</td>
<td>6.8±1.0</td>
</tr>
<tr>
<td>VS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>5.7±1.0</td>
<td>5.4±1.2</td>
</tr>
<tr>
<td>Apical</td>
<td>5.5±1.1</td>
<td>5.1±1.0</td>
</tr>
</tbody>
</table>

*p<0.01 vs. Sw1 along the short-axis and Sw2 along the short- and long-axes

Sw1 and Sw2, peak first and second systolic wall motion velocities, respectively; Q-Sw1, time from the Q wave of the electrocardiogram to the peak of the Sw1; PW, left ventricular posterior wall; VS, ventricular septum.
Fig. 2. Changes in clinical, M-mode and 2-dimensional echocardiographic variables after angiotensin II infusion. SBP, systolic blood pressure; LVDd and LVDs, left ventricular end-diastolic and end-systolic dimension, respectively; %FS, percent fractional shortening of the left ventricle; EF, left ventricular ejection fraction.

Fig. 3. Changes in peak first and second systolic motion velocities of the left ventricular wall after angiotensin II infusion. PW, left ventricular posterior wall; VS, ventricular septum; closed square, peak first systolic motion velocity (Sw1) at the basal region; closed circle, Sw1 at the apical region; open square, peak second systolic motion velocity (Sw2) at the basal region; open circle, Sw2 at the apical region.
Sw1 for the LV walls along the short- and long-axes were greater in the apical regions compared to those in the basal regions.

**Reproducibility of measurements**

The interobserver variability was 4.2% for Sw1, 5.8% for Sw2, and 5.0% for Q-Sw1. Intraobserver variability was 3.6% for Sw1, 4.4% for Sw2, and 4.8% for Q-Sw1.

**Discussion**

It is known that an increase in afterload affects LV systolic and diastolic function [1-5, 9-11]. In general, an increase in regional LV wall stress results in a decrease in regional LV contraction and a prolongation in the time constant from the LV pressure decay at isovolumic diastole (i.e. impaired LV relaxation). However, no consensus has been reached on the sequence of appearance of these changes. LeWinter et al. [2] demonstrated that a decrease in the LV myocardial shortening during an increase in afterload occurs in the base of the heart, but not in the region from the middle of the LV wall to the apex. In contrast, Liedtke et al. [1] reported that the administration of methoxamine to increase afterload produced akinesis in the LV apical region in a canine model. Miura et al. [5] also emphasized that significant LV asynchrony developed in the apical region during an increase in afterload.

Because these studies were performed in experimental models, various factors, such as the influence of anesthesia and thoracotomy, differences in the degree of increases in afterload, or technical differences appear to be involved in the discrepancy concerning the sites of origin of asynchrony.

Thus, we attempted to evaluate systolic LV asynchrony during an increase in afterload in normal individuals using pulsed tissue Doppler imaging [6, 7], which has been used recently in the clinical setting. This modality has the advantage of being easily acquired, but also of allowing quantitative analysis of regional LV wall motion in the short- and long-axis directions without being relatively influenced by preload [7, 12]. Oki et al. [13] investigated the influence of an increase in afterload due to angiotensin II infusion on LV wall motion using pulsed tissue Doppler imaging in healthy subjects, and emphasized its clinical usefulness.

In the present study, increasing the afterload with angiotensin II infusion resulted in significant changes in the systolic parameters of the LV walls. These changes appeared from the LV apical regions at low angiotensin II doses of 0.01 to 0.02 µg/kg/min. These
results indicate that systolic LV asynchrony occurs even in normal hearts during increased afterload, and are in agreement with previous studies [4, 5].

A histologic study [14] demonstrated an anatomic vulnerability in the apical region, which has a thinner wall and is sparse in myocardial fibers, compared with other regions. Therefore, it has been hypothesized that the apical region is most susceptible to regional wall stress, and prone to a decrease in contraction during increased afterload. In addition, changes in systolic pulsed tissue Doppler variables were more marked in the LV posterior wall than in the ventricular septum. As reported earlier [7, 12], the wall motion of ventricular septum is more susceptible to the effects of altered right-sided cardiac hemodynamics compared with that of the posterior wall. Therefore, changes in systolic pulsed tissue Doppler variables are greater in the posterior wall, which more accurately reflects LV contraction characteristics in healthy subjects with no regional wall motion abnormalities.

In a study using pulsed tissue Doppler imaging, Oki et al. [12] found that Sw1 along the long-axis and Sw2 along the short-axis reflect contraction of longitudinal fibers and circumferential fibers, respectively. In particular, Sw1 along the long-axis is considered to reflect myocardial contractility more sensitively [15], and the greatest change after angiotensin II was observed in Sw1 along the long-axis in the present study as well. On the other hand, many studies demonstrated the disarrangement of coordinated timing related to mechanical activation of LV walls using M-mode echocardiography [16], tissue Doppler imaging [17-19], and myocardial strain imaging [20, 21]. Our results also revealed that times from the beginning of the Q wave of the electrocardiogram to the peak first systolic velocity of the LV walls were markedly prolonged in the apical region compared to the basal region during angiotensin II infusion.

These results indicate that decreases in peak systolic velocities and prolonged timing of mechanical activation in systolic LV wall motion during increased afterload occurs in the apical region of the heart, resulting in LV asynchrony even in healthy subjects. Therefore, it is of clinical importance that an increase in blood pressure worsens the contractility of the apical wall because of its anatomic vulnerability in patients with anterior myocardial infarction or hypertrophic cardiomyopathy with asymmetric septal hypertrophy. Pulsed tissue Doppler imaging is easy to perform and useful in detecting LV asynchrony and is a promising tool for clinical applications in the future.

**Limitations**

First, LV wall motion was evaluated in only four sites of the LV wall. However, all subjects in the present study were healthy and had no regional wall motion abnormalities at baseline. Therefore, we believe that the results of the present study reflect the changes in the entire LV. The second limitation relates to the pharmaceutical action of angiotensin II on myocardial cells. Angiotensin II is generally thought to have a weak positive inotropic effect in normal hearts [22], but several investigators have described other potential actions, such as a negative inotropic effect [23, 24], a biphasic effect [25, 26], or no effect [27]. Therefore, a direct inotropic effect of angiotensin II cannot be excluded.

**References**

10. Schafer S, Fiedler VB, Thamer V. Afterload dependent


