Effect of Dobutamine on Regional Diastolic Left Ventricular Asynchrony in Patients With Left Ventricular Hypertrophy
— On-Line Quantification Using Automated Segmental Motion Analysis System —

Jinyao Liu, MD; Kazuya Murata, MD; Takashi Fujino, MD; Kayo Ueda, MD; Kazumi Kimura, MD; Yasuaki Wada, MD; Rikimaru Oyama, MD; Nobuaki Tanaka, MD*; Masunori Matsuzaki, MD

Dobutamine improves systolic as well as diastolic function, but its effect on left ventricular (LV) asynchrony is unknown. An on-line automated segmental motion analysis (A-SMA) system was developed, based on an automatic border detection technique, to evaluate the effect of dobutamine on LV asynchrony in patients with LV hypertrophy (LVH). Low dose (5 µg·kg⁻¹·min⁻¹) dobutamine stress echocardiography was performed in 15 patients with LVH and in 15 healthy subjects. Short-axis LV views were obtained and divided into 4 wedge-shaped segments using A-SMA. The time–area curve and its first derivative curve in each segment were displayed. Total normalized peak filling rates (nPFR) were obtained. Systolic and diastolic asynchronies were assessed from the coefficient of variation (CV) of the regional time intervals from end diastole to the peak ejection rate (T-PER), and from end systole to the peak filling rate (T-PFR), respectively. At baseline, the CV of T-PER and T-PFR in patients with LVH were greater than those in healthy subjects (CV-T-PER: 18.8±9.2 vs 9.6±4.3%, CV-T-PFR: 19.5±7 vs 8.1±4.1%, both p<0.01). During dobutamine infusion, differences among groups at baseline disappeared and systolic and diastolic asynchronies improved (CV-T-PER: 7.3±4.8 vs 5.7±2.1%, CV-T-PFR: 6.8±3.5 vs 5.1±1.3%, both p>0.05). Total nPFR increased (from 3.2±1.0/s to 5.6±1.3/s, p<0.01) with dobutamine infusion in patients with LVH. Dobutamine improved LV diastolic asynchrony, as evaluated by A-SMA, in patients with LVH demonstrating that the lusitropic effect of dobutamine improved LV regional diastolic asynchrony, playing an important role in the improvement of global LV diastolic filling. (Circ J 2003; 67: 119–124)

Key Words: Dobutamine; Echocardiography; Left ventricular asynchrony; Left ventricular hypertrophy
LV mass index \(\text{LVMI} (\text{g} \cdot \text{m}^{-2}) = \text{LVM} / \text{body surface area}\) was calculated using Devereux and Reichek’s\(^{10}\) and Teichholz’s rule, respectively, of 4 sectors. The CV was calculated by the following equation: \(\text{CV} = \frac{\text{standard deviation}}{\text{mean value}}\) × 100%.

The transmitral flow (TMF) velocities were recorded from an apical window during pulsed Doppler echocardiography by placing a 2-mm sample volume between the tips of the mitral leaflet. From the TMF velocity tracing, peak early (E) and late (A) diastolic filling velocities, E/A ratio, deceleration time of early filling (DT), and isovolumetric relaxation time (IRT) were measured. All measurements were obtained from 3 cardiac cycles and averaged.

Automated Segmental Motion Analysis (A-SMA)

Two-D images were obtained in the mid-papillary parasternal short axis at the end of expiration. Image quality and gain settings for endocardial tracking were optimized, and then the A-SMA system was activated. Briefly, after determining the region of interest around the LV cavity, the cavity was divided into 4 equiangular wedge-shaped sectors originating from the visually defined center of the LV end-systolic cavity (Fig 1A). Images were obtained at a frame rate of 30 per second. The time–area curves (Fig 1B) and their first derivative curves (Fig 1C) were automatically displayed in each sector in real time. Using the first derivative curve, the following indexes were obtained in each of the 4 sectors: (1) peak ejection and filling rates normalized by end-diastolic area (nPER, nPFR; \(\text{s}^{-1}\)), and (2) time to PER (T-PER; ms) and time to PFR (T-PFR; ms). The T-PER was the time interval from end-diastole to the timing of PER, and T-PFR was from end-systole to the timing of PFR. End diastole was determined at the R wave in ECG, and end systole was determined at the beginning of the second heart sound.

Evaluation of LV Asynchrony

Systolic and diastolic asynchronies were assessed by the coefficient of variation (CV) of T-PER and T-PFR, respectively, of 4 sectors. The CV was calculated by the following equation: \(\text{CV} = \frac{\text{standard deviation}}{\text{mean value}}\) × 100%.

Dobutamine Stress Echocardiography

A-SMA images were obtained at baseline and during dobutamine infusion. To obtain the same center of LV end-systolic cavity, the echo probe was fixed as similar position as possible before and during the dobutamine infusion. After baseline recording, dobutamine (5 \(\text{µg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\)) was administrated intravenously for 3 min. LV M-mode, transmitral flow recording and A-SMA images were obtained, and blood pressure and 12-lead ECG were monitored throughout the study.

Statistical Analysis

Data are presented as mean ± SD. The unpaired t test was used to compare results in control subjects and in patients with LVH. The Student’s t test was used to compare results before and after dobutamine stress echocardiography. The continuous variables among 4 sectors were tested with one-way analysis of variance (ANOVA) as appropriate. When an F value was significant by ANOVA, the Student-Newman-Keuls post hoc test was used for multiple comparisons. Differences yielding a probability value of \(p<0.05\) were considered to be statistically significant. Statistical analysis was performed using StatView for Windows version 5.0 (SAS Institute Inc, 1998, Cary, NC, USA).

Table 1 Characteristics of the Study Group

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n=15)</th>
<th>LVH patients (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±12</td>
<td>64±8</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>121±16</td>
<td>156±27*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>68±12</td>
<td>86±18*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>66±6</td>
<td>63±11</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>165±38</td>
<td>225±32*</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>8.1±1.1</td>
<td>13±1.3*</td>
</tr>
<tr>
<td>LVPWT (mm)</td>
<td>7.8±0.8</td>
<td>12±1.2*</td>
</tr>
<tr>
<td>Data are presented as mean ± SD. *p&lt;0.01 vs control subject. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; IVST, interventricular septal wall thickness; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index.</td>
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</table>
Results

Patient Characteristics

The baseline characteristics in the patients with LVH and the control subjects are summarized in Table 1. In the LVH group, the systolic and diastolic blood pressures were greater than those of the control group because of the selection criteria; the thicknesses of the interventricular septal and posterior walls, as well as the LVMI, were also greater in the LVH group.

Effects of Dobutamine on LV Global Systolic and Diastolic Function Assessed by 2-D and Doppler Echocardiography (Table 2)

At baseline, there were no differences in LVEF between the 2 groups. In contrast, isovolumetric relaxation and deceleration times were longer, and the E/A ratio smaller, in patients with LVH compared with the control subjects.

During dobutamine infusion, isovolumetric relaxation and deceleration times shortened in both groups and the difference between the 2 groups at baseline disappeared. LVEF increased in both groups, and the velocity of E and A increased in patients with LVH; however, the E/A ratio increased only in the control group.

Effects of Dobutamine on Global Systolic and Diastolic Filling Evaluated by A-SMA (Table 3)

At baseline, the value of nPFR was smaller and T-PFR was longer in patients with LVH than in the control subjects. The value of nPER and T-PER of global LV were similar in both groups at baseline. After intravenous dobut-
**Effects of Dobutamine on LV Asynchrony**

The representative first derivative curves of the time–area curves of each of the 4 segments at baseline and during dobutamine infusion using A-SMA are shown in Fig 2. At baseline, T-PER and T-PFR in the 4 sectors in control subjects were relatively uniform; in contrast, the nonuniformity in both T-PER and T-PFR in patients with LVH was remarkable. After dobutamine infusion, the nonuniformity in both T-PER and T-PFR in patients with LVH lessened. The changes in the CV in T-PER and T-PFR before and after dobutamine infusion are summarized in Table 4 and Fig 3. After dobutamine infusion, the CV of T-PER and T-PFR in both groups decreased, and the difference in the CV of T-PER and T-PFR disappeared (Fig 3). T-PER and T-PFR in each of the 4 segments before and during dobutamine infusion are plotted in Fig 4. T-PFR in the septal region in patients with LVH was longer than in healthy subjects at baseline, but after dobutamine infusion, this difference disappeared.

**Discussion**

In patients with LV hypertrophy, diastolic properties are impaired even when systolic performance is preserved. LV nonuniformity is an important determinant of LV diastolic dysfunction because it delays LV relaxation and thus impairs diastolic filling. LV asynchronies have been evaluated by left ventriculography, radionuclide angiography, and echocardiography, but none of these methodologies provides real-time evaluation. In this study, we have shown the diastolic asynchrony in patients with LVH using our newly developed A-SMA system, which uses an on-line system for analyzing color kinesis images, thus enabling us to quantify regional wall motion in real time. Further, using this system, we have shown that dobutamine improved global LV diastolic filling by improving LV diastolic nonuniformity in the hypertensive heart.

**Influence of LV Asynchrony on Global LV Diastolic Filling**

Prior studies have shown that LV diastolic asynchrony is associated with deterioration of LV early filling and impaired isovolumetric relaxation in patients with dilated cardiomyopathy or coronary artery disease. Vignon et al used off-line analysis of color kinesis images to demonstrate that in patients with concentric hypertrophy there was delayed diastolic regional endocardial motion in at least 1 segment, but that diastolic endocardial motion was relatively uniform in all segments in normal subjects.

In the present study, we used A-SMA, which can identify temporal deviations of regional endocardial motion as asynchronic, to assess the effects of asynchrony on total diastolic function. Accompanying the increased CV of T-PER and T-PFR, prolongation of LV isovolumetric relaxation and reduced LV diastolic filling were observed in the hypertrophied left ventricle. Thus, LV diastolic asynchrony also leads to impairment of LV relaxation and filling in patients with LVH.

**Possible Mechanism of LV Asynchrony**

It appears reasonable to suppose that both heterogeneous interstitial fibrosis and its localized foci are the major anatomical mechanisms of increasing asynchrony in the hypertrophied left ventricle. The nonuniform inactivation is secondary to the loss of contractile elements and normal intercellular connections, and the consequently increased...
diastolic wall motion nonuniformity, in the hypertrophied left ventricle. Prior studies have shown that prolongation of decay time with increasing end-systolic pressure is exacerbated as contractility falls. Another study showed that the LV time constant correlated well with the amount of the nonuniformity, which is responsible for the systolic loading dependent relaxation. Previous studies have reported that both LV hypertrophy and increased afterload of LV are related to LV asynchrony. In the present study, despite the elevation of systolic blood pressure during dobutamine infusion, asynchrony improved in both groups, so we hypothesized that LV asynchrony in mild LV hypertrophy caused by hypertension is more closely related to LV hypertrophy itself than to increased afterload.

**Effects of Dobutamine on LV Asynchrony**

Previous studies demonstrated that β-adrenergic receptor stimulation accelerated myocardial relaxation, which related to the positive lusitropic effects of dobutamine and that the LV time constant improved in both normal subjects and in patients with dilated cardiomyopathy.

In the present study, dobutamine enhanced both segmental myocardial contraction and relaxation in patients with LV hypertrophy, and improved both systolic and diastolic nonuniformity. This improvement might be related to the positive inotropic and lusitropic effects of dobutamine. LV contraction is related to relaxation through intracellular mechanisms such as calcium cycling. In the intact heart, enhanced contractility results in heightened elastic restoring forces in the myocardial wall, which accelerates isovolumetric relaxation. The energy stored in the myocardium during systole is increased and then released during diastole; this elastic recoil contributes most importantly to ventricular pressure relaxation and LV pressure decay during dobutamine infusion. Therefore, the possible mechanism of the improvement of LV asynchrony by dobutamine is that the elevation of cyclic adenosine monophosphate enhances ejection as well as regulating myocardial relaxation.

**Study Limitations**

Similar to other studies based on an automated boundary detection system, data analysis using A-SMA depends on the quality of the 2-D echo images and the operator-defined gain settings. Additionally, in our system, tissue harmonic imaging was not available and should be added to the A-SMA system in order to improve endocardial boundary detection. Because the frame rate of the A-SMA system was limited to 30 frames/s, the temporal resolution may not have been good enough for measuring the timing of peak ejection or peak filling. Some of these limitations can be overcome by using higher frame-rate imaging in conjunction with extended color scale and automated gain settings. Moreover, the lower frame rate might not allow an accurate enough definition of endocardial motion at high heart rates during dobutamine infusion. However, no significant differences in heart rate were present before or during low-dose dobutamine infusion in the present study subjects. Thus, heart rate is unlikely to have affected our results. We used only the parasternal short-axis projection for evaluating LV asynchrony, which differs from previous studies that assessed LV asynchrony using radionuclide angiography or left ventriculography techniques, and thus we could not evaluate the long-axis view. In the apical view, the segment containing the mitral valve may appear to have an inadequate change in area. Therefore, it was difficult to acquire echo images from several approaches.

**Conclusions**

The A-SMA system allowed us to characterize LV diastolic asynchrony in real time in patients with LVH. Our data demonstrated that the lusitropic effect of dobutamine improved LV regional diastolic asynchrony, which played an important role in the improvement of global LV diastolic filling.

**References**

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