GLOBAL AND REGIONAL DIASTOLIC FILLING DYNAMICS IN COMPENSATED DILATED CARDIOMYOPATHY

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To assess the left ventricular (LV) global and regional (anterior, apical, inferior) diastolic filling dynamics in compensated dilated cardiomyopathy (DCM), we measured left ventricular pressure and instantaneous volume from angiography in 7 normal controls (CTL) and 6 DCM patients with sinus rhythm. Global and regional peak filling rate (PER), time constant of LV pressure decline (T; Weiss's method) and LV chamber stiffness (k; Gaasch's method) were calculated. In DCM, left ventricular end-diastolic volume (ml/m²) was larger than in CTL (137±29 vs. 74±6, p<0.001), and stroke index (ml/m²) was not different from CTL (46±14 vs. 46±8, NS), indicating a compensated state of LV. Mitral valve opening pressure (mmHg) tended to increase in DCM compared with CTL (12±6 vs. 8±4). Global PFR (ml/sec/m²) (CTL=216±47 vs. DCM=201±36) and k (CTL=0.044±0.023 vs. DCM=0.029±0.016) were not different between 2 groups. However, T (msec) was markedly prolonged in DCM compared with CTL (61±10 vs. 35±5, p<0.001). In CTL, regional PFR (1/sec) showed almost the same values in each region, but in DCM, apical region showed higher PFR than in other regions. Thus, early diastolic filling might play an important role in maintaining the total transmitral flow in DCM despite severe impairment of LV relaxation. This compensation could be related mainly to accelerated regional lengthening of the LV apical region.

LEFT ventricular early diastolic filling is a complex phenomenon and is influenced by a combination of factors such as relaxation, atrial reservoir function, left ventricular compliance, and mitral valve function. Recent experimental study documented that left ventricle accommodated a higher percentage of its total stroke volume during early diastole during the volume overload of mitral regurgitation. Numerous studies evaluating the indices such as time constant, peak negative dP/dt, and negative dP/dt upstroke pattern during isovolumic relaxation period have demonstrated that left ventricular relaxation was severely impaired in dilated cardiomyopathy. Therefore, it is postulated that the left ventricular rapid filling, which follows isovolumic relaxation period in the cardiac cycle, is disturbed in dilated cardiomyopathy with severely impaired left ventricular function.

Key words:
Dilated cardiomyopathy
Time constant
Peak filling rate
LV chamber compliance

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ventricular relaxation.

Several investigators have tried to find the relationship between left ventricular relaxation and filling. However, they failed to show a close relationship between the two. Accordingly, to determine whether or not the peak filling in dilated cardiomyopathy is disturbed, and if not, to clarify its compensating mechanisms during diastole, we analyzed the left ventriculograms frame-by-frame with simultaneously recorded high fidelity left ventricular pressure, and evaluated the global and regional diastolic parameters.

METHODS

Patient Selection
Patient population consisted of 7 normal and 6 dilated cardiomyopathy (DCM) patients, who have undergone routine cardiac catheterization using a Millar’s catheter-tip micromanometer Model PC-484A (Millar Instruments Inc., Houston, Texas). Seven normal subjects were selected from among 50 normal patients, and 6 patients were chosen from 32 DCM patients because they had good opacification of the left ventricle and high quality pressure tracings. All DCM patients were in normal sinus rhythm and had no conduction disturbances. NYHA class of all DCM patients was I or II. Ages in the control group (49 ± 9 years) were not significantly different from those in the DCM group (51 ± 12). The diagnoses of the normal subjects were all atypical chest pain, which was confirmed by chest X-ray, electrocardiogram, echocardiogram, exercise tolerance test with radionuclide scintigram, routine hemodynamic parameters, left ventriculography, and coronary angiography with ergonovine provocation test. The diagnosis of idiopathic dilated cardiomyopathy was based on the criteria of the National Study Group of Idiopathic Cardiomyopathy of Japan and the report of the WHO/ISFC task force. Endocardial biopsy of the left and/or right ventricles was performed in all patients with cardiomyopathy, and histological examination revealed characteristic features such as interstitial fibrosis, cellular hypertrophy, and myocardial cell degeneration.

Catheterization Procedure
The patients underwent cardiac catheterization in the fasting state following 10 mg of diazepam premedication. All cardioactive medications were withheld for at least 48 hours before the procedure. A Millar’s catheter-tip micromanometer was then introduced into the aorta and left ventricle via the right brachial artery. After measuring the aortic and left ventricular pressures at rest, left ventriculograms from 30° right anterior oblique were obtained at

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Fig.1. Representative examples of pressure tracing in normal control (upper panel) and DCM patient (lower panel). During the left ventriculography, ECG, PCG, dP/dt, cine pulse, and high- and low-gain left ventricular pressure were recorded simultaneously. In DCM, peak negative dP/dt is markedly decreased and the negative dP/dt upstroke pattern is downward convex (indicated by an arrow) in contrast with that of normal, suggesting the severe impairment of left ventricular relaxation.

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60 frames/sec with a Siemens Cardoskop U (Siemens Inc., Erlangen, West Germany). Forty milliliters of Urografin-76 (Schering Inc., Berlin, West Germany) were injected into the left ventricle at a rate of 14 ml/sec at the end of normal inspiration using an injector Angiomat 3000 (Liebel-Flarsheim Inc., Cincinnati, Ohio). Frame numbers, ECG signal, and the first derivative of left ventricular pressure (dP/dt) were superimposed on each cine film. DP/dt on each cine film allowed us to measure the pressure and volume precisely16 During the left ventriculography, the electrocardiogram, phonocardiogram, DP/dt, cine pulse, and high- and low-gain left ventricular pressure were simultaneously recorded on an Electronics for Medicine VR-12 recorder (Electronics for Medicine Inc., Pleasantville, New York) at a paper speed of 150 mm/sec (Fig. 1). The micromanometer system was calibrated against a mercury column before insertion, and then during the measurement the output from the micromanometer was adjusted to the pressure measured through the fluid channel of this catheter by means of a Statham P23 ID transducer (Gould Inc., Oxnard, California). The zero pressure reference was obtained at the mid-chest level. DP/dt was obtained from the R-C differentiating circuit (Analog data processor model V4202, Electronics for Medicine, Inc.) and was calibrated by a known slope. Left ventricular volumes were derived serially from consecutive frames of the cineventriculogram using standard area-length methods17 by SICOR cath-lab computer system (Siemens-Elema Inc. Solna, Sweden).

Data Analysis and Calculation

Hemodynamic Parameters

Routine hemodynamic parameters were calculated. End-diastole was defined as the time of dP/dt crossing to zero after the A-wave. End-systole was defined as the time 20 msec before the peak negative dP/dt. Diastolic time was defined as the time interval between end-systole and end-diastole. Mean circumferential fiber shortening (meanVcf) was calculated as follows18: meanVcf=(Ced-Ces)/(Ced·ET), where Ced=end-diastolic equatorial circumference, Ces=end systolic equatorial circumference, and ET=ejection time, which was calculated as the time interval between peak positive and negative dP/dt. Left ventricular ejection fraction was defined as the ratio of the stroke volume to the end-diastolic volume multiplied by 100.

Global Diastolic Parameters

The time constant was calculated according to the method of Weiss et al19 The left ventricular pressure during isovolumic relaxation period was digitized with a handheld planimeter (Cardias GP-3000A, Nac Inc., Tokyo, Japan) at 5 millisecond intervals from the time of peak negative dP/dt to the time of mitral valve opening. The time of mitral valve opening was defined as the time when the first negative jet appeared in the left ventricle. The left ventricular pressure during isovolumic relaxation period was fitted by the method of least squares to the function P=Ae−V/T (P: left ventricular pressure, A:constant), and from that the time constant (T) was derived. Isovolumic relaxation time (IRT) was determined as the interval between 20 msec before the peak negative dP/dt of time of mitral valve opening. The first derivative of left ventricular volume curve (dP/dt) was obtained by a 5-point Lagrangian interpolation method20 Peak filling rate was defined as peak positive dV/dt21 Time interval between mitral valve opening and peak filling was also measured. To obtain elastic modulus of chamber stiffness (k), high-fidelity left ventricular diastolic pressure was digitized serially at 16.7 msec intervals from the high-gain left ventricular pressure recording at intervals synchronized precisely with each ventriculographic frame. Simultaneous left ventricular pressure-volume coordinates during diastole were analyzed by fitting to a monoexponential function, P=AeκV (P: left ventricular pressure, A:constant, V: left ventricular volume), according to the method by Gaasch et al22 Left ventricular distensibility at end-diastole was calculated as dV/dP=1/kP22

Regional Diastolic Parameters

Regional parameters were driven from the time interval between mitral valve opening and peak filling in each region [t (MVO-PF)], regional peak filling rate (PFR), and
TABLE I HEMODYNAMIC PARAMETERS

<table>
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<tr>
<th></th>
<th>CONTROL</th>
<th>DCM</th>
<th>p</th>
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<tr>
<td>HR (beat/min)</td>
<td>67 ± 14</td>
<td>63 ± 18</td>
<td>ns</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>131 ± 15</td>
<td>122 ± 16</td>
<td>ns</td>
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<tr>
<td>LVEDP (mmHg)</td>
<td>8 ± 3</td>
<td>14 ± 7</td>
<td>ns</td>
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<tr>
<td>(+) dP/dt (mmHg/sec)</td>
<td>1631 ± 251</td>
<td>1030 ± 281</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(-) dP/dt (mmHg/sec)</td>
<td>1945 ± 275</td>
<td>830 ± 212</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PMVO (mmHg)</td>
<td>8 ± 4</td>
<td>12 ± 6</td>
<td>ns</td>
</tr>
<tr>
<td>Pmin (mmHg)</td>
<td>1 ± 2</td>
<td>8 ± 3</td>
<td>&lt;0.001</td>
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<td>DT (msec)</td>
<td>540 ± 164</td>
<td>616 ± 264</td>
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</tr>
<tr>
<td>mVcf (l/sec)</td>
<td>1.20 ± 0.12</td>
<td>0.61 ± 0.71</td>
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<td>EDVI (ml/m²)</td>
<td>74 ± 6</td>
<td>137 ± 29</td>
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</tr>
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<td>ESVI (ml/m²)</td>
<td>29 ± 5</td>
<td>92 ± 22</td>
<td>&lt;0.001</td>
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<tr>
<td>SI (ml/m³)</td>
<td>46 ± 8</td>
<td>46 ± 14</td>
<td>ns</td>
</tr>
<tr>
<td>EF (%)</td>
<td>61 ± 7</td>
<td>33 ± 7</td>
<td>&lt;0.001</td>
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</table>

HR = heart rate; LVSP = left ventricular peak systolic pressure; LVEDP = left ventricular end-diastolic pressure; (+) dP/dt = peak positive dP/dt; (-) dP/dt = peak negative dP/dt; PMVO = left ventricular pressure at mitral valve opening; Pmin = left ventricular minimal diastolic pressure; DT = diastolic time interval; mVcf = mean circumferential fiber shortening velocity; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; SI = stroke index; EF = ejection fraction.
Values are mean ± SD.

Asynchrony index (AI) in each region. To obtain these parameters, left ventriculogram taken from a 30° right anterior oblique projection was divided into 3 regions frame-by-frame: anterior (ANT), apical (APX) and inferior (INF). Namely, the long axis was drawn by connecting the mid of the aortic valve and apex, and trilsection of the axis by transverse chords gave 6 areas.

Then neighboring 2 areas at antero-lateral region, apical region, and inferobasal region were combined and treated as 1 region and named anterior, apical and inferior, respectively. Instantaneous area changes in each region (S cm²) were calculated by a SICOR cath-lab computer system and the first derivative of the area change curve (dS/dt) in a cardiac cycle was generated. Regional PFR (l/sec) was obtained as the peak positive dS/dt normalized by the end-diastolic regional area. Then, the time interval between mitral valve opening and peak positive dS/dt, or peak filling rate was calculated in each region. The asynchrony index (AT) was calculated as follows; AI=SOR [t_{ANT}-M] + (t_{APX}-M)^2 + (t_{INF}-M)^2 / 3, where t is regional t(MVO-PF) and M=(t_{ANT}+t_{APX}+t_{INF}) / 3.

**Statistical analysis**

Data are presented as mean±SD. A student’s unpaired t-test was employed for statistical comparisons of variables between control and DCM. One way analysis of variance was used for comparisons of variables among 3 regions (anterior, apical, inferior). The significance was considered at p value less than 0.05.

**RESULTS**

**Hemodynamic Parameters (Table I)**

Heart rate, left ventricular peak systolic pressure, and end-diastolic pressure showed no significant difference between the control and DCM. The end-diastolic volume index was significantly larger in the DCM group, 137±29 ml/m² compared with 74±6 ml/m² for the control group, p<0.001. However, the stroke volume index in the DCM group was not significantly different from the control group, 46±14 versus 46±8 ml/m², indicating a compensated state in DCM patients. The ejection fraction in the DCM group was markedly diminished, 33±7% compared with 61±7% for the controls. Peak positive dP/dt and mean velocity of circumferential fiber shortening in the DCM

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<table>
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<tr>
<th>Global</th>
<th>CONTROL</th>
<th>DCM</th>
<th>p</th>
</tr>
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<tr>
<td>T (msec)</td>
<td>35 ± 5</td>
<td>61 ± 10</td>
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<td>IRT (msec)</td>
<td>98 ± 11</td>
<td>162 ± 40</td>
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<tr>
<td>t (MVO-PF) (msec)</td>
<td>69 ± 26</td>
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<td>(+) dV/dt (ml/sec)</td>
<td>357 ± 75</td>
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<td>(+) dV/dt/EDV (l/sec)</td>
<td>2.91 ± 0.55</td>
<td>1.51 ± 0.41</td>
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<td>(+) dV/dt/BSA (ml/sec/m^2)</td>
<td>216 ± 47</td>
<td>201 ± 36</td>
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<td>k</td>
<td>0.044 ± 0.023</td>
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<td>(dV/dP) ed (ml/mmHg)</td>
<td>3.66 ± 1.51</td>
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<table>
<thead>
<tr>
<th>Regional</th>
<th>ANT</th>
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<td>t (MVO-PF) (msec)</td>
<td>74 ± 37</td>
<td>122 ± 81</td>
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<tr>
<td>(msec) INF</td>
<td>67 ± 36</td>
<td>72 ± 27</td>
<td>ns</td>
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<tr>
<td>AI (msec)</td>
<td>43 ± 16</td>
<td>61 ± 45</td>
<td>ns</td>
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<tr>
<td>PFR (l/sec)</td>
<td>23 ± 10</td>
<td>37 ± 25</td>
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<tr>
<td>ANT</td>
<td>2.68 ± 0.81</td>
<td>1.54 ± 0.42</td>
<td>&lt;0.05</td>
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<tr>
<td>APX</td>
<td>2.88 ± 1.03</td>
<td>1.90 ± 0.32*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>INF</td>
<td>2.56 ± 0.66</td>
<td>1.31 ± 0.58</td>
<td>&lt;0.01</td>
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</table>

\[ T = \text{time constant}; \ IRT = \text{isovolumic relaxation time}; \ t (MVO-PF) = \text{time interval between mitral valve opening and peak filling}; \ (+) dV/dt = \text{peak positive } dV/dt; \ (+) dV/dt/EDV = \text{peak positive } dV/dt \text{ normalized by end-diastolic volume}; \ (+) dV/dt/BSA = \text{peak positive } dV/dt \text{ normalized by body surface area}; \ k = \text{stiffness constant}; \ (dV/dP) ed = \text{distensibility index at end diastole}; \ AI = \text{asynchrony index}; \ PFR = \text{peak filling rate}; \ ANT = \text{anterior region}; \ APX = \text{apical region}; \ INF = \text{inferior region}. \]

Values are mean ± SD; *p < 0.05 APX vs INF.

Group, 1030 ± 281 mmHg/sec and 0.61 ± 0.71 l/sec, respectively, were significantly reduced compared to 1631 ± 251 mmHg and 1.20 ± 0.12 l/sec for the control group, p < 0.01, suggesting depressed contractility in these patients. Diastolic time in the DCM group, 616 ± 264 msec, was slightly prolonged but not significantly in comparison to 540 ± 164 msec for the controls. Left ventricular pressure at the mitral valve opening tended to increase in DCM but not significantly, 12 ± 6 mmHg compared to 8 ± 4 mmHg for the controls. Left ventricular minimum pressure showed a significant increase in the DCM group, 8 ± 8 mmHg compared to 1 ± 2 mmHg in the control group, p < 0.001.

**Global Diastolic Parameters (Table II)**

As shown in Fig.1, the dP/dt upstroke pattern during isovolumic relaxation period in DCM patients lost its exponential nature and became downward convex. This suggests that left ventricular relaxation is severely impaired in these patients according to the report from our laboratory. Time constant and isovolumic relaxation time showed marked prolongation in the DCM group, 61 ± 10 and 162 ± 40 msec, respectively, as compared to 35 ± 5 and 98 ± 11 msec for the control group (Table II).

Left ventricular pressure-volume relations during diastole in a normal subject and DCM patient are shown in Fig.2. Significant downward and rightward displacement of the pressure-volume relation in the DCM group is noted. The elastic modulus of the left ventricular chamber stiffness (k) tends to be smaller in DCM group, 0.029 ± 0.016 as compared to 0.044 ± 0.023 for the control group, but there was no statistical significance. The distensibility index, (dV/dP)ed, in DCM (3.85 ± 2.07 ml/mmHg) also did not show significant difference as compared to the control (3.66 ± 1.51 ml/mmHg). These findings indicate that the left ventricular operational compliance in DCM is at least not

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Fig. 2. Left ventricular pressure-volume relations during diastole in normal subject and DCM patient are shown. Closed circles represent actual data points and solid lines indicate fitted exponential function by least-squares technique. The r value for the curve fitting in the normal group was 0.98 and that in DCM was 0.97. Significant downward and rightward displacement of pressure-volume relation in DCM was noted in this case.

Fig. 3. Examples of left ventricular volume curves and its first derivative, \( \frac{dV}{dt} \), in normal control (left panel) and DCM patient (right panel). Volume curves are plotted from peak negative \( \frac{dP}{dt} \) to end-diastole. Note that peak positive \( \frac{dV}{dt} \) or peak filling rate in DCM is almost the same value as that of the control.

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lower than in normal control.

Left ventricular volume curves and its first derivative, dV/dt, in a normal control and a DCM patient are shown in Fig. 3. Peak positive dV/dt or peak filling rate in DCM showed almost the same value as that of the control. The time interval between mitral valve opening and peak filling in the DCM group, 67 ± 46 msec, was not significantly different from that of the control group, 69 ± 26 msec (Table II and Fig. 4). Peak positive dV/dt normalized by left ventricular end-diastolic volume was significantly lower in DCM, 1.51 ± 0.41 l/sec compared to 2.91 ± 0.55 l/sec in the control group, p < 0.001. Meanwhile, when this index was not normalized by end-diastolic volume, there was no significant difference in peak positive dV/dt between DCM and control group, 310 ± 69 versus 357 ± 75 ml/sec. Peak positive dV/dt normalized by the body surface area also showed no significant difference between DCM and normal control, 201 ± 36 versus 216 ± 47 ml/sec-m² (Table II and Fig. 5).

Regional Diastolic Parameters (Table II)

There were no significant differences in the time interval between mitral valve opening and peak filling between normal and the DCM group in each region. In the DCM group, the time interval between mitral valve opening and peak filling of the apical region, 72 ± 27 msec, was not prolonged compared to 67 ± 36 msec in the control, however, other regions tended to have longer values than the control group (Table II and Fig. 4). Regional peak filling rate (l/sec) in the DCM group showed lower values in all regions as compared to the control group. In the peak filling rate in the apical region (1.90 ± 0.32) was higher than those in the other 2 regions (anterior: 1.54 ± 0.42, inferior: 1.31 ± 0.58). However, significance was only observed between the apical and inferior regions (Table II and Fig. 5). Asynchrony index tended to be larger in the DCM group, 37 ± 25 compared with 23 ± 10 msec for control group, but there was no statistical significance (Table II).
DISCUSSION

Global early diastolic filling.

In the present study, the peak filling rate (peak positive (+) dV/dt) of the left ventricle and the time interval between mitral valve opening and peak filling were found to be maintained at almost normal levels in DCM patients (Table II, Fig. 4 and 5). These findings suggest that the left ventricular filling pattern during early diastole is not impaired in DCM.

Previous studies on the early diastolic filling dynamics in DCM were done using cineventriculography$^{4,21}$ and pulsed Doppler echocardiography$^{24}$. Hammermeister et al$^{21}$ described the rate of change of the left ventricular volume in man, and they reported that the peak (+) dV/dt in normal (503±171 ml/sec) was not significantly different from that in cardiomyopathy (512±177 ml/sec), which were all nonobstructive cardiomyopathy with dilated, relatively thin-walled ventricles. When corrected by end-diastolic volume (EDV), the resultant peak (+) dV/dt/EDV was significantly depressed in all diseased patients whom they studied.

Their results agree with our present data showing that normalized peak filling rate in DCM was significantly lower than that in the control group (Table II). This is thought to be caused partly by the enlarged EDV in diseased hearts such as in DCM, which is also noted by Hammermeister et al in their investigation. Van de Werf et al$^{4}$ also studied the diastolic properties of the left ventricle in normal patients and in those with third heart sounds (S3s) including dilated cardiomyopathy. They obtained results identical to ours, that peak (+) dV/dt for control without S3s was not significantly different from DCM with S3s. They concluded that the presence of S3 was associated with an impaired relaxation or increased viscous resistance to the filling in cardiomyopathy patients.

On the contrary, Takenaka et al$^{24}$ demonstrated the abnormalities of peak diastolic mitral flow velocity in DCM patients without mitral regurgitation. They showed that peak mitral flow velocity in early diastole in DCM (31±11 cm/sec) was reduced compared to control (53±10 cm/sec). These flow velocity values do not equal the
absolute peak mitral flow volume, because the mitral orifice area in patients with dilated left ventricle might be different from normal subjects. Ross et al. demonstrated that the area of the mitral valve orifice averaged 28% less at end-systole than at end-diastole using the technique for rapid fixation of canine left ventricle. This area was 39% larger in the hearts subjected to overtransfusion than in those with normal filling pressure. Therefore, we must consider the cross-sectional area of the mitral annulus, for converting the mitral flow velocity to the transmitral flow volume particularly in the dilated left ventricle.

Rokey et al. showed that there were no significant differences in peak filling rate by Doppler echocardiography vs angiography when the peak filling rate was computed as early diastolic velocity multiplied by the cross-sectional area of the mitral annulus. Therefore, in compensated DCM, the early diastolic trans-mitral flow volume could be maintained to accommodate the stroke volume by the enlargement of chamber size and the mitral orifice area.

Regional early diastolic filling.

In the apical region of the DCM group, the present study has shown that the time interval between mitral valve opening and peak filling was not prolonged compared with that in the control group, and the peak filling rate was higher than those in the other regions. In the present study, we were interested in the mechanisms for maintaining the global early diastolic filling in DCM. Acceleration of the peak filling at the apex might be one of the factors for maintaining the global peak filling in DCM.

Few studies have been done to clarify the regional variation in diastolic filling patterns. Ling et al. studied chronically instrumented conscious dogs and documented that the apical transmural pressure and diameter increased more rapidly and reached diastasis 17±4 msec earlier than the corresponding mid-ventricular measurements. Klausner et al. described regional variations in average lengthening rates by measuring the lengthening of internal ventricular radii from the midpoint of long axis to various points along the endocardial surface in single-plane human angiograms. They found that lengthening rates of the apical wall were lower than proximal, middle and distal anterior wall during both rapid and slow filling phase. Because their definition of end-systole was not precise and the ventriculographic analysis is different from ours (chord vs area), we can not relate these measurements to our own. Lew et al. employed sonomicrometers in open-chest dogs to study lengthening of short segments of circumferentially oriented myocardium located at the base, midportion, and apex of the anterior left ventricular free wall. They observed that at lower left ventricular end-diastolic pressure, the peak lengthening rate (dl/dt) was greatest at the apex, and regional differences in dl/dt diminished as left ventricular end-diastolic pressure increased. Although their acute experimental data can not be related directly to our clinical study, we can understand that DCM with normal end-diastolic pressure is compensating by increased peak dl/dt at the apex.

Relation between PFR and relaxation or compliance

Left ventricular early diastolic filling may be influenced by phasic left ventricular relaxation rate, atrial reservoir function, left ventricular dynamic compliance, and mitral valve function. In the present study, left ventricular relaxation in DCM was severely impaired according to indices such as the time constant and isovolumic relaxation time (Table II) agreeing with our previous reports and others. Furthermore, the negative dP/dt upstroke pattern during isovolumic relaxation period in DCM patients showed a downward convex pattern in contrast with upward convex pattern in normal controls (Fig. 1), indicating the impairment of the left ventricular relaxation in DCM. On the other hand, the chamber compliance of the left ventricle, estimated from "stiffness constant: k" and "dV/dt at end-diastole", was not significantly different from the normal control subjects (Table II). These results indicate that early diastolic trans-mitral flow in DCM is maintained at a normal level in compliant left ventricular chambers in spite of impairment of relaxation.

The experimental study by Ishida et al.
demonstrated that there was a weak correlation between rapid filling rate and time constant ($r = -0.369$). The clinical study by Magorien et al\textsuperscript{13} also showed a weak correlation between time constant and peak filling rate ($r = -0.499$). Meanwhile, Fioretti et al\textsuperscript{12} demonstrated that the time constant of relaxation correlated inversely with the left ventricular early diastolic inflow rate normalized by volume at the minimal diastolic pressure ($r = -0.72$) in patients with coronary artery disease. We think that the normalization caused a high correlation between time constant and peak filling rate in their study, because left ventricular volume at minimal diastolic pressure tends to increase in diseased hearts with prolonged time constant. Combining our present data with others, we believe that there is a weak relationship between relaxation and filling. Ishida et al\textsuperscript{10} have recently shown that the left atrium-left ventricular pressure gradient is an important determinant for left ventricular filling during early diastole. Although, we have not measured the left atrium-left ventricular pressure gradient in the present study, it could have increased in proportion to the higher mitral valve opening pressure in DCM than in controls (Table 1). The higher mitral opening pressure might have also contributed to the maintenance of left ventricular early diastolic filling in DCM. Grossman et al\textsuperscript{30} demonstrated that a good correlation existed between peak negative dP/dt and diastolic distensibility. Also their data suggested that early diastolic left ventricular relaxation was impaired in DCM associated with a decrease in LV diastolic compliance. In their study population of DCM patients, left ventricular end-diastolic pressure was markedly higher and cardiac index was lower compared with those in the present study population. We consider that DCM patients under compensated state examined in the present study had enough normal chamber compliance to accommodate the early diastolic filling volume.

Intensive investigations have been done concerning the relation between left ventricular asynchrony and relaxation\textsuperscript{31–33} however, there are only a few studies on the relationship between the left ventricular asynchrony and the filling dynamics. Bonow et al\textsuperscript{34} examined the regional left ventricular asynchrony in patients with hypertrophic cardiomypathy (HCM) by using radionuclide ventriculography. They noted that the patients with HCM had greater regional variation in both timing and magnitude of rapid filling, and verapamil reduced these regional variations. They concluded that the beneficial effects of verapamil on the left ventricular diastolic function in HCM may be mediated by a reduction in regional asynchrony. In our study, regional asynchrony in DCM showed no significant increase compared with that in control, suggesting that the maintained global early diastolic filling in compensated DCM might be due to the low asynchronicity of the regional left ventricular dynamics during early diastole.

Limitations of the present study.

Potential limitations to our method should be considered. First, we used a single-plane cineventriculogram for the measurement of left ventricular volume. It might be the cause of error for the derived indicies from left ventricular volume such as global and regional peak filling rate. Asynchrony index was also calculated only by referring to the right anterior oblique view. This index might be calculated as higher in DCM, if the left anterior oblique view was included in our measurements. The second possible restriction is the analysis of regional wall by the area method. Ingels et al\textsuperscript{35} showed a "wringling motion" of the left ventricle, with the major transverse diameters of the apex and base rotating 12° in opposite directions from end-diastole to end-systole. Therefore, shortening or lengthening measurement obtained from single-plane angiograms, which were taken in our present study, may not represent motion of the same area.

Conclusions

In diseased hearts like DCM with dilated left ventricular chamber, global early diastolic filling was preserved when cardiac pump function was compensated, i.e., forward stroke volume was kept normal, even though the relaxation was severely impaired. Factors such as enlargement of mitral orifice area, accelerated regional
lengthening of the apical region, normal operational chamber compliance, elevated mitral valve opening pressure, and low asynchronicity were suggested as causes of this compensation.

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