EFFECT OF AFTERLOAD ON THE LEFT VENTRICULAR PRESSURE FALL DURING ISOVOLUMIC RELAXATION PERIOD IN MAN

KAZUHIRO KATAYAMA, M.D., TOSHIKAKU KUMADA, M.D., MASUNORI MATSUZAKI, M.D. TAKASHI FUJI, M.D., MICHIIRO KOHNO, M.D., HIROSHI OGAWA, M.D. 
MASAHARU OZAKI, M.D., YASUO MATSUDA, M.D. AND REIZO KUSUKAWA, M.D.

To assess the effect of afterload on the left ventricular pressure (LVP) fall during isovolumic relaxation period (IRP) in man, we examined the peak \(-dP/dt\), \(-dP/dt\) upstroke pattern in IRP, and time constant (T) in 15 patients [normal (N) : 5, valvular heart disease (VHD) : 5, dilated cardiomyopathy (DCM) : 5]. LVP and echocardiographic internal diameter were measured simultaneously at rest and after about 30 mmHg increment of LV peak systolic pressure (PSP) by drip infusion of angiotensin (20 ng/kg/min). After augmentation in afterload, heart rate (HR) increased slightly in VHD. T increased significantly (p < 0.05) in N (from 32 ± 3 to 39 ± 4 ms) and DCM (from 56 ± 18 to 72 ± 12 ms), but not in VHD (from 41 ± 5 to 46 ± 8 ms) probably due to increased HR. LV end-systolic dimension had the same trend as T. Although there was no significant change in peak \(-dP/dt\) in N (from 1937 ± 385 to 1945 ± 189 mmHg/s), VHD (from 1521 ± 210 to 1730 ± 462 mmHg/s), or DCM (from 814 ± 143 to 814 ± 131 mmHg/s), the \(-dP/dt\) upstroke pattern during IRP became nonexponential in N and more downward convex in VHD or DCM. Thus, these changes of T and \(-dP/dt\) upstroke pattern suggest the afterload dependence of LVP fall during IRP in normal and diseased hearts.

RECENT studies from our laboratory\(^1\)\(^-\)\(^5\) have shown that the left ventricular pressure (LVP) fall during isovolumic relaxation period (IRP) in diseased hearts lost its exponential nature, and this was reflected on the negative dP/dt upstroke pattern during IRP. However, the effect of afterload on the LVP fall during IRP in the intact and diseased human left ventricle is still controversial.

Parmley and coworkers\(^6\) first described the afterload dependence of relaxation using papillary muscle preparations. Other investigators also supported this fact\(^7\)\(^-\)\(^9\). The afterload independence of time constant (T) has been shown using isolated heart preparations\(^10\) right-heart bypass preparations\(^11\) and anesthetized dogs\(^12\). Meanwhile, the afterload dependence of T has been demonstrated using conscious dogs\(^13\) and anesthetized dogs\(^14\). The afterload dependence of peak negative dP/dt has been shown by several authors\(^13\)\(^-\)\(^17\).

Although the afterload dependence of relaxation in the papillary muscle is documented\(^6\)\(^-\)\(^9\), the dependence in the intact left ventricle has not been confirmed yet. Accordingly, we examined the effect of afterload on the left ven-

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Key words:
- Left ventricular relaxation
- Left ventricular function
- Time constant

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The Division of Internal Medicine, Yamaguchi University School of Medicine, Yamaguchi, Japan
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Mailing address: Kazuhiro Katayama, M.D. Division of Internal Medicine, Yamaguchi University School of Medicine, 1144 Kogushi, Ube, Yamaguchi 755, Japan

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tricular relaxation in intact as well as diseased human hearts using indices such as peak negative dP/dt and T, and we also evaluated the upstroke pattern of negative dP/dt during IRP.

METHODS

Patients
The patient population consisted of 8 men and 7 women, mean age 49 years (range 33–68 years). All subjects were in sinus rhythm except for 2 patients, one of whom was VHD with atrial fibrillation and the other was DCM with RV pacing. Five normal subjects (N), mean age 48 ± 9 years, were considered to have normal left ventricular function based on clinical and catheterization findings.

In 5 subjects of valvular heart disease (VHD), mean age 46 ± 10 years, 4 were mitral stenosis (MS) with minimum mitral regurgitation, and 1 was MS with minimum aortic regurgitation. Mean mitral valvular gradient (MVG) of these subjects was 11 ± 3 mmHg and mean valvular area (MVA) was 1.9 ± 1.0 cm².

In 5 patients with dilated cardiomyopathy (DCM), mean age 51 ± 11 years, the ejection fraction (EF) was less than 50%. Endocardial biopsy of the left and/or right ventricle was performed in all patients with cardiomyopathy. Histological examination revealed a variety of abnormalities such as interstitial fibrosis, cellular hypertrophy, and myocardial cell degeneration. The diagnosis of primary myocardial disease was based on the criteria of the National Study Group of Idiopathic Cardiomyopathy of Japan and the report of the WHO/ISFC task force on the definition and classification of cardiomyopathies.

Methods
After obtaining the informed consent, diagnostic right- and left- heart catheterization was performed in the postabsorptive state, approximately 30 min after premedication with diazepam (Horizon®) of 10 mg by intramuscular injection. All other medications had been discontinued 24 hours before the study. After the diagnostic part of the investigation, the LVP was measured at equilibrium conditions by a Millar’s catheter-tip transducer (Model PC-471 #7F) and was recorded.
TABLE I

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Heart rate (beat/min)</th>
<th>LVEDP (mmHg)</th>
<th>Peak LVSP (mmHg)</th>
<th>Peak dP/dt (+) (mmHg/sec)</th>
<th>Peak dP/dt (−) (mmHg/sec)</th>
<th>T (msec)</th>
<th>Dd (mm)</th>
<th>Ds (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>C 48 ± 9</td>
<td>78 ± 13</td>
<td>8 ± 3</td>
<td>133 ± 19</td>
<td>1563 ± 123</td>
<td>1937 ± 385</td>
<td>32 ± 3</td>
<td>51 ± 2</td>
</tr>
<tr>
<td></td>
<td>A 72 ± 9</td>
<td>15 ± 5†</td>
<td>168 ± 23†</td>
<td>1508 ± 189</td>
<td>1945 ± 189</td>
<td>39 ± 4†</td>
<td>54 ± 2†</td>
<td>38 ± 2†</td>
</tr>
<tr>
<td>VHD</td>
<td>C 46 ± 10</td>
<td>68 ± 11</td>
<td>10 ± 4</td>
<td>121 ± 16</td>
<td>1255 ± 234*</td>
<td>1521 ± 210</td>
<td>41 ± 5**</td>
<td>50 ± 4</td>
</tr>
<tr>
<td></td>
<td>A 77 ± 12†</td>
<td>16 ± 4†††</td>
<td>157 ± 14†††</td>
<td>1439 ± 249†</td>
<td>1730 ± 462</td>
<td>46 ± 8</td>
<td>49 ± 5</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>DCM</td>
<td>C 51 ± 11</td>
<td>69 ± 12</td>
<td>15 ± 10</td>
<td>107 ± 10*</td>
<td>897 ± 332**</td>
<td>814 ± 143***</td>
<td>56 ± 18*</td>
<td>70 ± 5***</td>
</tr>
<tr>
<td></td>
<td>A 72 ± 12</td>
<td>24 ± 6†††</td>
<td>130 ± 13†††</td>
<td>924 ± 285</td>
<td>814 ± 131</td>
<td>72 ± 12†</td>
<td>70 ± 8</td>
<td>62 ± 10†</td>
</tr>
</tbody>
</table>

LVEDP = left ventricular end-diastolic pressure; Peak LVSP = peak left ventricular systolic pressure; peak (+) dP/dt = peak positive dP/dt; peak (−) dP/dt = peak negative dP/dt; T = time constant; Dd = left ventricular end-diastolic dimension; Ds = left ventricular end-systolic dimension; N = normal control; VHD = valvular heart disease; DCM = dilated cardiomyopathy; C = control; A = angiotensin.

* = p < 0.05, ** = p < 0.01, *** = p < 0.001 VHD or DCM vs N
†† = p < 0.05, ††† = p < 0.01, †††† = p < 0.001 A vs C

Fig. 2. Percent change in heart rate (HR) and left ventricular end-diastolic dimension (Dd) in normal (N), valvular heart disease (VHD), and dilated cardiomyopathy (DCM) during normal (Normal) and angiotensin infusion. Significantly increased in VHD and DCM compared with control state.
Fig. 3. Percent changes in time constant and negative dP/dt peak values in normal (N), valvular heart disease (VHD), and dilated cardiomyopathy (DCM) during angiotensin infusion compared with control state are shown. After augmentation in afterload, time constant increased significantly in N and DCM, but peak negative dP/dt showed no significant change in all three groups.

of Weiss et al.\textsuperscript{10} and 5 consecutive beats were averaged. The average correlation for the fitted curves of 150 examined beats to compute $T$ was 0.994.

For statistical comparisons of the various variables, the Student's t-test was employed and significance was considered at values of $p$ less than 0.05.

RESULTS

Table I summarizes hemodynamic data obtained before and during angiotensin infusion in each group. At rest there were no significant differences in age, heart rate, and left ventricular end-diastolic pressure (LVEDP) between N and VHD or DCM. Peak left ventricular systolic pressure (LVSP) in DCM was lower than in N (133 ± 19 vs. 107 ± 10 mmHg, $p < 0.05$). Peak positive (+)dP/dt in VHD (1225 ± 234 mmHg/sec) and DCM (897 ± 332 mmHg/sec) showed lower ($p < 0.05$) values than normal (1563 ± 123 mmHg/sec). Peak negative (−)dP/dt in DCM (814 ± 143 mmHg/sec) was lower ($p < 0.001$) than in N (1937 ± 385 mmHg/sec), but not in VHD. T in VHD (41 ± 5 msec) and DCM (56 ± 18 msec) were larger ($p < 0.05$) than in N (32 ± 3 msec). In DCM, both end-diastolic and end-systolic dimensions (70 ± 5 and 59 ± 9 mm, respectively) were significantly ($p < 0.001$) larger values than in N (51 ± 2 and 35 ± 2 mm). After augmentation in afterload by angiotensin infusion, LVEDP and peak LVSP were significantly elevated in all three groups. In VHD, heart rate (68 ± 11 to 77 ± 12 beat/min) and peak (+)dP/dt (1255 ± 234 to 1439 ± 249 mmHg/sec) significantly ($p < 0.05$) increased compared with control resting values (Table I and Fig. 2). Although there were no significant changes in peak (−)dP/dt in N, VHD, or DCM, T in N (32 ± 3 to 39 ± 4 msec) and DCM (56 ± 18 to 72 ± 12 msec) was significantly ($p < 0.05$) prolonged (Table I and Fig. 3). Left ventricular end-diastolic dimension increased only in N group (51 ± 2 to 54 ± 2 mm, $p < 0.05$) (Table I). Left ventricular end-systolic dimension increased in N (35 ± 2 to 38 ± 2 mm, $p < 0.05$) and DCM (59 ± 9 to 62 ± 10 mm, $p < 0.05$), but not in VHD (Table I and Fig. 2). The mean correlation of the linear regression between natural logarithm $P$ and time in N, VHD, and DCM before and during angiotensin infusion being always calculated larger than 0.99, meanwhile the (−)dP/dt upstroke pattern during IRP became nonexponential in N, and more downward convex in VHD and DCM during increasing afterload (Fig. 4).

DISCUSSION

When we use the time constant of LVP fall during IRP as an index of left ventricular relaxation in various heart diseases, exponentiality of the LVP decay and the effect of loading condition on LVP fall should be examined. We have already demonstrated that LVP fall during IRP in the diseased heart might be nonexponential.\textsuperscript{1-5} Recently, Martin and coworkers\textsuperscript{20} also described the same question. We further thought that afterload dependence for $T$ documented by some investigators might be the results of the deviation from the resting exponential decline of LVP.
during IRP after afterload increment.

At resting state, decreased value of peak LVSP in DCM and low values of peak (+)dP/dt in VHD and DCM might be caused by the depressed contractility. Low values of peak (-)dP/dt and prolonged T in VHD and DCM suggest the relaxation disturbance in these groups agreeing with the report by Hirota et al.\textsuperscript{21} (Table I).

Afterload dependence of peak (-)dP/dt in the intact heart was demonstrated by several authors.\textsuperscript{13–17} In our study, after augmentation in afterload, peak (-)dP/dt tended to increase in N and VHD. However, in DCM, peak (-)dP/dt showed no change (Table I and Fig. 3). After augmentation in afterload, T significantly increased in N and DCM, but no significant change was shown in VHD, probably due to the increased heart rate (Fig. 2 and 3). If the left ventricular pressure falls exponentially during IRP \( (P = e^{At} + B; A \) and \( B \) are constants), the first derivation of LVP (or negative dP/dt upstroke) should also be exponential \( (dP/dt = Ae^{At} + B) \). In the present study, normal subjects had exponential upstroke of the negative dP/dt (Fig. 4). However, in the diseased heart such as VHD and DCM, the negative dP/dt upstroke pattern showed downward convex suggesting the non-exponential fall of LVP during IRP (Fig. 4). These findings were consonant with our previous reports.\textsuperscript{1,3} To calculate T, we have to hypothesize that LVP falls exponentially during IRP. Whatever, the r values were high (mean r values were 0.994 in our present study), LVP fall during IRP itself lost its exponential nature as detected by negative dP/dt upstroke pattern. There are currently 2 methods to calculate T. One is without asymptote (Weiss's method\textsuperscript{10}) and the other is with asymptote (Thompson's method\textsuperscript{22}). We chose Weiss's method temporarily, because discussion about the choice of the formula is meaningless,
unless the LVP fall during IRP is really exponential. As the afterload was increased, the negative dP/dt upstroke pattern lost its exponential nature in N and became more downward convex in VHD and DCM (Fig. 4), corresponding with the prolongation of T. In addition, it had been shown that the negative dP/dt downward convex in the diseased heart became upward or straight after the reduction of afterload (unpublished data). These findings suggest the afterload dependence of LVP fall during IRP.

Underlying mechanisms for the load dependence of relaxation is still not precisely known. Gaasch et al. have demonstrated a direct relation between T and systolic pressure and length. They mentioned that the mechanical restoring forces might influence the rate of pressure decline in the intact heart in the same way as a squeezed tennis ball snaps back to its original size and shape. As shown in Fig. 2, end-systolic dimension of LV in N and DCM increased significantly and in VHD slightly (due to increased HR) after augmentation in afterload. These increased end-systolic dimensions might have caused the prolongation of T. Recent study by Hori et al. demonstrated that the time course of systolic loading conditions, rather than the peak left ventricular pressure, may primarily regulate the ventricular relaxation rate. Although it is difficult to determine whether this mechanism is functioning or not in our clinically based human study, we can speculate that the peripheral arterial impedance could be altered, with which the loading sequence of the ventricle is changed, by angiotensin infusion in normal as well as in diseased human left ventricle. Our data showed that the load dependence of relaxation (percent increase of T) in DCM was almost the same as in N and somewhat smaller in VHD than in N (Fig. 3). LeCarpentier et al. have documented that the intracellular calcium-sequestering systems exist efficiently enough to preserve the homeostasis of load sensitivity of relaxation during cardiac hypertrophy and heart failure in rat left ventricular papillary muscle. On this experimental basis, there could be an effective calcium-accumulating system (presumably the sarcoplasmic reticulum) in the diseased human left ventricle, because the load dependency of relaxation was shown to be maintained in this present study.

In conclusion, the negative dP/dt upstroke pattern during IRP was exponential in normal subjects (meaning that the LVP fall during IRP is exponential) and downward convex in patients with valvular heart disease and dilated cardiomyopathy (meaning that LVP fall during IRP is nonexponential). When the afterload was augmented by angiotensin, LVP fall during IRP became nonexponential in normal hearts and deviated from the nonexponential decline in the diseased hearts, judging from the pattern of negative dP/dt upstroke, and this resulted in an increase in time constant. These results suggest an afterload dependence of relaxation in normal as well as in diseased human left ventricle.

REFERENCES

10. WEISS JL, FREDERIKSEN JW, WEISFELDT ML: Hemodynamic determinants of the time-course of


