STUDIES ON THE MONOEXPONENTIAL NATURE OF THE LEFT VENTRICULAR PRESSURE FALL DURING ISOVOLUMIC RELAXATION PERIOD IN THE DISEASED HEART

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Our recent clinical studies on the negative dP/dt upstroke pattern suggested that the left ventricular pressure (LVP) deviated from the exponential curve during isovolumic relaxation period (IRP) in diseased hearts. To examine this further two types of monoexponential curve fitting were done in various heart diseases (normal (N): 8, angina pectoris (AP): 8, myocardial infarction (MI): 13, hypertrophic cardiomyopathy (HCM): 10, dilated cardiomyopathy (DCM): 8). LVP was measured by a Millar’s catheter-tip transducer, and four types of time constant (T1-T4) were derived: T1 was calculated by an exponential curve fitting \( e^{-t/T_1} + B \) (B is constant), T2 by the ratio \( Pm/\text{peak} \), \( dP/dt \) (Pm is LVP at peak \( dP/dt \)), T3 by the best exponential curve fit \( e^{-t/T_3} + B + C \) (C is constant), and T4 by the ratio \( (Pm-C)/\text{peak} \). If the exponential curve fitting was reasonable, the relation between T1 and T2, or T3 and T4, should be on the line of identity. The result was as follows: T2 = 1.4 T1 - 6.1 (r = 0.84) and T4 = 1.1 T3 - 10.7 (r = 0.94). Additionally, C (mmHg) in MI (-26 ± 15), HCM (-36 ± 19) and DCM (-32 ± 20) were lower \( p < 0.05 \) than in N (-13 ± 7). These findings suggest that the LVP during IRP could deviate from the monoexponential curve and that careful attention should be given to calculate the time constant in diseased hearts.

INFORMATION on the left ventricular relaxation is very important for understanding the hemodynamics in various heart diseases. Recently the time constant (T) has been popular as an index of left ventricular relaxation. However, the monoexponential of the left ventricular pressure (LVP) fall during isovolumic relaxation period (IRP) as the basis for calculating T has been controversial. Weiss et al demonstrated the possibility to fit the LVP fall during IRP to the exponential function, \( e^{-t/T} + B \) (B is constant), and Karlner et al showed that T could be calculated by the absolute value of peak negative \( dP/dt \) and the LVP at peak \( dP/dt \), provided the LVP fall is exponential. Meanwhile, Kumada et al showed the impairment of LVP fall during IRP caused by the acute experimental myocardial ischemia. The clinical study also showed that the exponential nature of

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- Time constant
- Negative dP/dt
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TABLE I  HEMODYNAMIC PARAMETERS

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<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>Pm (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL CONTROL</td>
<td>8</td>
<td>44 ± 11</td>
<td>70 ± 9</td>
<td>9 ± 2</td>
<td>121 ± 8</td>
<td>1578 ± 186</td>
<td>1730 ± 209</td>
</tr>
<tr>
<td>AP</td>
<td>8</td>
<td>52 ± 8</td>
<td>69 ± 11</td>
<td>7 ± 4</td>
<td>151 ± 22†</td>
<td>1737 ± 555</td>
<td>1937 ± 330</td>
</tr>
<tr>
<td>MI</td>
<td>12</td>
<td>55 ± 11*</td>
<td>68 ± 14</td>
<td>15 ± 6*</td>
<td>125 ± 20</td>
<td>1279 ± 360*</td>
<td>1185 ± 227§</td>
</tr>
<tr>
<td>HCM</td>
<td>10</td>
<td>48 ± 11</td>
<td>68 ± 17</td>
<td>12 ± 5</td>
<td>124 ± 32</td>
<td>1535 ± 549</td>
<td>1228 ± 400†</td>
</tr>
<tr>
<td>DCM</td>
<td>8</td>
<td>53 ± 10</td>
<td>73 ± 9</td>
<td>14 ± 9</td>
<td>117 ± 23</td>
<td>940 ± 295§</td>
<td>883 ± 214§</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; Pm = left ventricular pressure at peak (-) dP/dt; AP = angina pectoris; MI = myocardial infarction; HCM = hypertrophic cardiomyopathy; DCM = dilated cardiomyopathy.

*p < 0.05 vs control; † p < 0.01 vs control; ‡ p < 0.001 vs control.

Values are mean ± SD. A student t-test was used to determine p values.

TABLE II  4 TYPES OF TIME CONSTANT AND C VALUES

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>T1 (msec)</th>
<th>T2 (msec)</th>
<th>T3 (msec)</th>
<th>T4 (msec)</th>
<th>C (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL CONTROL</td>
<td>8</td>
<td>33 ± 5</td>
<td>32 ± 5</td>
<td>49 ± 8</td>
<td>39 ± 8</td>
<td>-13 ± 7</td>
</tr>
<tr>
<td>AP</td>
<td>8</td>
<td>31 ± 6</td>
<td>37 ± 8</td>
<td>56 ± 11</td>
<td>53 ± 14*</td>
<td>-20 ± 9</td>
</tr>
<tr>
<td>MI</td>
<td>12</td>
<td>46 ± 8§</td>
<td>56 ± 12§</td>
<td>81 ± 20§</td>
<td>79 ± 19§</td>
<td>-26 ± 15*</td>
</tr>
<tr>
<td>HCM</td>
<td>10</td>
<td>41 ± 13</td>
<td>55 ± 19†</td>
<td>89 ± 39*</td>
<td>89 ± 44†</td>
<td>-36 ± 19†</td>
</tr>
<tr>
<td>DCM</td>
<td>8</td>
<td>53 ± 12§</td>
<td>77 ± 16§</td>
<td>100 ± 37†</td>
<td>116 ± 43§</td>
<td>-32 ± 20*</td>
</tr>
</tbody>
</table>

T1 = time constant calculated by Weiss's method (8); T2 = time constant calculated by dividing Pm by peak (-) dP/dt; T3 = time constant calculated by the best fit e^(-T3) + B + C (B and C are constant); T4 = time constant calculated by the ratio (Pm-C)/peak (-) dP/dt (Pm: LVSP at peak (-) dP/dt); C = asymptote of the curve e^(-T3) + B + C.

Abbreviations for AP, MI, HCM, and DCM and the symbols for significance are the same as Table I.

LVP fall during IRP was lost in the diseased heart3−6. To examine the monoexponentiality of LVP fall during IRP in the diseased heart, we have fitted the LVP during IRP to the two types of exponential function and four types of T (T1−T4) were derived. T1 was calculated by an exponential curve fitting e^(-T1) + B, T2 by the ratio Pm/peak (-) dP/dt (Pm is LVP at peak (-) dP/dt). T3 by the best exponential curve fit e^(-T3) + B + C (B and C are constant) and T4 by the ratio (Pm-C)/peak (-) dP/dt. If the two curve fittings (e^(-T1) + B, e^(-T3) + B + C) were adequate, the relation between T1 and T2 or between T3 and T4 should be located on the line of identity. Under this hypothesis we compared the four types of T and examined the applicability of using monoexponential function to fit the LVP during IRP in diseased heart.

METHODS

[Patients]

The patient population consisted of 39 men and 7 women, mean age 51 years (range 40–62 years) (Table I and II). The diagnosis of the normal control (N) were all atypical chest pain, which was confirmed by chest X-ray, electrocardiogram, echocardiogram, routine hemodynamic parameters, left ventriculography, and coronary angiography. There were eight cases of angina pectoris (AP), four stable effort and four spontaneous. Typical histories were taken...
in all eight cases. Three of 4 patients with stable effort AP had single vessel disease and the fourth patient had two vessel disease. In patients with spontaneous AP, who had normal coronary arteries by the coronary arteriogram at rest, significant coronary spasm of 75% or greater, S-T elevation, and chest pain were induced by ergonidine malate infusion during cardiac catheterization. The data in this group were taken at the basal state.

The clinical diagnosis of myocardial infarction (MI) was based on the history, the electrocardiogram, serum enzymes [GOT, LDH, CPK including myocardial band (MB)], and coronary arteriogram. Of the twelve patients with MI, nine had anteroseptal MI, two had antero-septal with inferior MI, and one had inferior MI. Coronary arteriogram showed one vessel disease in six, two vessel disease in five, and three vessel disease in one patient. Left ventriculography showed asynergy in all MI patients except in two cases. Significant stenosis of the coronary artery was defined by the presence of at least 75% narrowing luminal diameter in the major coronary arteries. The diagnosis of primary myocardial disease was based on the criteria of the National Study of Idiopathic Cardiomyopathy of Japan and the report of the WHO/ISFC task force. Eight of the ten patients with HCM had asymmetrical septal hypertrophy (ASH) and two had apical hypertrophy. In eight cases with dilated cardiomyopathy (DCM), the ejection fraction (EF) was less than 50%. Endocardial biopsy of the left and/or right ventricles was performed in all.

\[
P = e^{At+B}, \quad \dot{P} = AP
\]

\[
T_1 = -1/A \quad \text{(Weiss's method)}
\]

\[
T_2 = P_m/\dot{P}_m
\]

\[
P = e^{At+B} + C, \quad \dot{P} = A(P-C)
\]

\[
T_3 = -1/A
\]

\[
T_4 = (P_m-C)/\dot{P}_m
\]

Fig.1. Filter response characteristics. It responded linearly up to 20 Hz by 20 dB/decade.

Fig.2. Time constant (T1) was calculated according to the method of Weiss et al., and time constant (T2) was obtained as the ratio of \( P_m \) to \( \dot{P}_m \) (left panel). Time constant (T3) was computed by the method of Thompson et al., and time constant (T4) was obtained as the ratio of \( (P_m-C) \) to \( \dot{P}_m \) (right panel). \( P \) = left ventricular pressure (LVP); \( A, B \), and \( C \) = constants, \( \dot{P} = dP/dt \), \( P_m = LVP \) at peak \(-\) dP/dt; \( \dot{P}_m \) = value of peak \(-\) dP/dt. Arrow indicates the end of isovolumic relaxation period (IRP).
patients with cardiomyopathy, and typical abnormalities were confirmed by histological examination.

[Methods]
After obtaining informed consent, diagnostic right- and left- heart catheterization was performed in the postabsorptive state, approximately 30 minutes after premedication with Diazepam (Horizon®) of 10 mg by intramuscular injection. All other medications had been discontinued at least 24 hours before the study. After recording the LVP, left ventriculography and coronary angiography were performed in all cases. Ergonovine maleate was given 0.2 mg i.v. only in the cases in which variant AP was suspected before cardiac catheterization. The LVP was measured at equilibrium conditions by a Millar's catheter-tip transducer (Model PC-471 #7F) and recorded on an Electronics for Medicine VR-12 recorder at a paper speed of 150 mm/sec. The micromanometer system was calibrated against a mercury column before insertion, and then during measurement the output from the micromanometer was adjusted to the pressure measured through the fluid channel of this catheter by means of a Statham P23ID transducer. The first derivative of the LVP \( \frac{dP}{dt} \) was obtained from the R-C differentiating circuit (Analog data processor model V4202, Electronics for Medicine, Inc.) and was calibrated by a known slope. The high frequency cut filter of the differentiator was 25 Hz, and it showed linear response up to 20 Hz by 20 db/decade (Fig. 1). The LVP during IRP was digitized with a hand-held planimeter (GP-3000A, NAC Inc.) at 5 millisecond intervals from the time of peak \((-\frac{dP}{dt})\) to the time when LVP fell to the same level as the preceding left ventricular end-diastolic pressure. The time constant (T1) was calculated according to the method of Weiss et al. and 5 consecutive beats were averaged (Fig. 2). The correlation \( r \) of the linear regression between natural logarithm \( P \) and time was also calculated. The average correlation for the fitted curves of over 200 examined beats was 0.99. The LVP during IRP was fitted by the method of least squares to the function

\[
P = e^{At} + B
\]

Therefore, the following equations can be derived: \( \frac{dP}{dt} = Ae^{At} + B = \frac{AP}{\tau} \times P \) (where the time constant \( T \) is defined by \( T = -\frac{1}{A} \)). Thus at any pressure during IRP, \( \frac{dP}{dt} \) is a function of time constant. Provided the time of peak \((-\frac{dP}{dt})\) is zero \( t = 0 \) sec, the following relationship can be obtained according to the above analysis:

\[
T = -\frac{1}{A} = -\left[ P_t = 0/(\frac{dP}{dt})_t = 0 \right] = P_t = 0/\text{peak} (-\frac{dP}{dt})
\]

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Fig. 5. Representative example of 1 nP vs. time in a normal subject (left) and a patient with dilated cardiomyopathy (DCM) (right). Negative dP/dt upstroke pattern was shown in each case. Time constant (T) by Weiss's method in DCM is computed larger than that of normal. Although the r values are the same, the negative dP/dt upstroke pattern in DCM has lost its exponential nature. 

\[ \ln P = \text{natural logarithm of left ventricular pressure} \]

Time constant can be calculated, if both the peak (−) dP/dt and LVP at \( t = 0 \) (Pm) are known, the time constant so obtained was averaged at 5 consecutive beats and was defined as T2 (Fig. 2).

It was found that \( e^{At + B} + C \) (C is constant) was a better formula for fitting the LVP during IRP. In this study the Fletcher-Powell's method was used to fit the LVP during IRP to this formula. The software programed in digital computer (FACOM 230–28) enabled us to find the parameter A, B and C when the value of the diagnostic function \( I = \sum_{i=1}^{N} \left[ y - (e^{At + B} + C) \right]^2 \) (y: sampled values of LVP during IRP every 5 millisecond intervals) is minimum. The time constant (T3) and C were calculated according to the above method and 5 consecutive beats were averaged (Fig. 2). The average correlation for the fitted curves of over 200 examined beats was 0.99. When the formula \( P = e^{At + B} + C \) can be held, the following equations can be derived: \( dP/dt = Ae^{At} + B = A (P - C) \). Provided the time of peak negative dP/dt is zero (t = 0), the following relationships can be obtained: \( P_t = 0 (Pm) = e^{B} + C \), \( dP/dt_t = 0 = Ae^{B} \). Thus, \( T = -1/A = -e^{B}/(dP/dt_t = 0) = (Pm-C)/\text{peak} \) (−) dP/dt. Time constant can be calculated from the value of peak (−) dP/dt and LVP at \( t = 0 \) (Pm) same as T2. The time constant so obtained was averaged at 5 consecutive beats and was defined as T4 (Fig. 2).
Fig. 7. Relationship between T3 and T4 in normal subjects and patients with various heart diseases. Solid line indicates the regression line: $T4 = 1.1T3 - 10.7$ ($r = 0.94$). Dotted line indicates the line of identity. Although most cases located near the line of identity, there was a tendency that T4 was calculated larger than T3 in a group such as normal which had lower T values, and calculated smaller than T3 in a group such as DCM which has higher T values.

For statistical comparisons of the variables, a student t-test was employed and significance was considered as P values of less than 0.05.

RESULTS

The hemodynamic parameters are summarized in Table I. There was no significant difference in heart rate between N and other patient groups. Age in MI (55 ± 11 years) was higher ($p < 0.05$) than in N (44 ± 11), the left ventricular end-diastolic pressure (LVEDP) in MI (15 ± 6 mmHg) was greater ($p < 0.05$) than in N (9 ± 2 mmHg), and peak left ventricular systolic pressure (LVSP) in AP (151 ± 22 mmHg) was greater ($p < 0.01$) than in N (121 ± 8 mmHg). No other statistically significant difference was observed in those three parameters between N and other patient groups. Peak positive (+) dP/dt and negative (−) dP/dt showed lower ($p < 0.05$) values in MI (1279 ± 360, 1185 ± 227 mmHg/sec, respectively) and DCM (940 ± 295, 883 ± 214 mmHg/sec) compared with N (1578 ± 186, 1730 ± 209 mmHg/sec). In HCM, only peak (−) dP/dt was lower (1228 ± 400 mmHg/sec, $p < 0.01$) than in N, but peak (+) dP/dt was maintained within normal range. In AP, both peak (+) and (−) dP/dt values showed no significant differences compared with N. Pm in AP (69 ± 16 mmHg) and DCM (66 ± 14 mmHg) were significantly higher ($p < 0.05$) than in N (54 ± 5 mmHg).

For types of time constant (T1–T4) and C values are summarized in Table II. All four types of T (T1, T2, T3 and T4 msec) showed greater
showed higher values in DCM patients than in normal ones, and the r values were more than 0.99 in both groups. However, in the diseased groups, the negative dP/dt upstroke pattern lost its exponential nature as shown in this figure. This indicates that in the diseased hearts LVP fall during IRP lost its exponential nature whatever the r values are high.

A notable correlation was found between T1 and T2 (T2 = 1.4 T1 − 6.1, r = 0.84, p < 0.001) (Fig. 6). As shown in this figure, all subjects except for 8 cases were located above or on the line of identity, indicating that T2 is calculated as larger than T1 computed by Weiss’s method. A correlation between T3 and T4 approached the line of identity (T4 = 1.1 T3 − 10.7, r = 0.94, p < 0.001) (Fig. 7). However, the value of intercept was larger than that of between T1 and T2.

In Figure 8, asymptote C values were compared between normal and other patient groups. C (mmHg) in MI (−26 ± 15), HCM (−36 ± 19) and DCM (−32 ± 20) patients were significantly higher (p < 0.05) than that in normal (−13 ± 7) patients.

**DISCUSSION**

Some investigators suggest that the impairment of relaxation may occur prior to that of contractility in various heart diseases. Therefore, detecting the relaxation abnormalities is valuable for the diagnosis and treatment of the diseased heart.

Time constant and peak negative dP/dt are now two major indices for assessing the left ventricular relaxation. Our data showed that peak (−) dP/dt in MI, HCM and DCM were significantly lower than in N (Table I), and time constant (T1) in MI and DCM or other types of time constant (T2, T3, T4) in MI, HCM and DCM were significantly higher than in N (Table II, Figs. 3 and 4). These findings indicate the disturbance of left ventricular relaxation in MI, HCM and DCM and correspond to reports by other investigators.

To assess the left ventricular relaxation, loading conditions such as heart rate, preload, afterload and contractility must be considered. Using different animal models, dependence of heart rate and contractility and independence of preload on T were documented experimentally by investigators. However, they do not agree on the afterload effect on...
In our study there were no significant differences in heart rate as it affects T between N and other patient groups. Increased preload in MI suggested by high LVEDP is also negligible, as documented by experimental studies. Decreased contractility in MI and DCM, indicated by low peak (+) dP/dt, might have caused the decreased values of T in these groups. The effect of increased afterload on relaxation in AP, in which peak LVSP had elevated, can not be evaluated, because T and peak (-) dP/dt showed no significant difference between N and AP.

If LVP (P) during IRP is expressed as a function of t; P = e\(^{At} + B\)(A and B are constant), time constant (T) can be defined by -1/A. T is the time needed for LV pressure to fall from its initial value to 1/e of that value. Therefore, T is calculated on the condition that LVP during IRP is exponential. Based on this hypothesis, three different ways of calculating T have been developed. The first method by Weiss et al. is to calculate T by fitting LVP during IRP using the method of least squares to the function; P = e\(^{At} + B\). In the second method by Karliner et al. T is the value of peak (-) dP/dt divided by the LVP at peak (-) dP/dt. The third method reported recently by Thompson et al. calculates T by fitting LVP during IRP to the monoeponential function with asymptote (P = e\(^{At} + B\) + C; C is constant).

Using isolated cat papillary muscle Parmley et al. noted that isometric relaxation could be divided into two phases, the first being an abrupt fall in tension, and the second, an exponential decline. Weiss et al. showed that the time course of isovolumic pressure fall subsequent to peak (-) dP/dt is exponential using isolated canine left ventricular preparations. From these experimental data, time constant in normal heart can be calculated by one of the three methods. Weissfeldt et al. demonstrated that incomplete relaxation did not occur if the next beat began more than 3.5 T after maximal negative dP/dt for the previous beat. This index has been used to identify incomplete relaxation in the experimental study by Lorell et al. and in the clinical setting by Carrol et al. However, in diseased hearts, whether the monoeponential function to fit LVP fall during IRP is applicable or not, has yet to be determined as has been pointed out by Martin et al.

Kumada et al. first described that the dyssynchronous contraction in ischemic and normal zones during the isovolumetric fall in LVP could greatly modify the maximum rate of pressure fall and its exponential nature in experimental study of acute coronary occlusion. We have recently suggested that impaired left ventricular relaxation disturbed the exponential fall of LVP during IRP (P = e\(^{At} + B\)) and reflected on the upstroke pattern of (-) dP/dt (dP/dt = Ae\(^{At} + B\)) . Moreover, the greater the discrepancy between T1 and T2 becomes, the more the LVP fall during IRP deviates from the exponential curve in the diseased heart. Based on these experimental and clinical studies, we examined the monoeXponential nature of LVP during IRP in the diseased heart by comparing T calculated form four different methods. If LVP during IRP is exponential, the relationship between T1 and T2 or T3 and T4 should be on the line of identity. However, in the present study, T2 was always calculated larger than T1 except in several cases (Table II and Fig. 5). This means that curve fitting without asymptote is inadequate in the diseased heart. Then we compared T3 and T4. Although T4 was calculated larger than T3 in the normal group with low T values, and calculated smaller than T3 in the group with DCM which has higher T values (Table II and Fig. 6), the relationship between T3 and T4 was more closer than that between T1 and T2. Yellin et al. reported that the conventional time constant (without asymptote) of monoeXponential pressure decline was still a useful index of relaxation, even though the ventricle relaxed to a lower pressure minimum (usually negative) in the completely isovolumic nonfilling cycle. The findings from our clinical study suggest that time constant is still a good index of relaxation, and that the exponential curve fitting with asymptote (Thompson’s method) was better than without asymptote (Weiss’s method). This contradiction in experimental data between Yellin et al. and us resulted from the nonexponential fall of LVP during IRP in the diseased heart. Asymptote C in MI, HCM and DCM were all lower than in N in our present study. The negativity and decreased values of asymptote in the patient with coronary artery disease was pointed out by Thompson et al., who showed that the asymptote value did not change significantly during pacing induced ischemia. The meaning of this asymptote needs further investigation.

The r values of two different ways of curve fitting (Weiss’s and Thompson’s methods) were above 0.99, but the pressure fall during IRP (P = e\(^{At} + B\)) could be nonexponential according

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to the downward upstroke pattern of the first derivative \( (dP/dt = Ae^{At} + B) \) in the diseased heart (Fig. 5). This nonexponential fall of LVP during IRP might modify the curve fitting data. We think that the relationship between T1 and T2 (T2 > T1) was affected by this phenomenon. Therefore, careful attention has to be given to the usage of the monoexponential curve fitting of LVP during IRP in the diseased heart.

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