ASSESSMENT OF LEFT VENTRICULAR FUNCTION IN ISCHEMIC HEART DISEASE
—The Relation between Pressure Decay during the Isovolumic Relaxation Phase and Regional Wall Motion Abnormality—

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We examine whether regional wall motion abnormality (RWMA) could contribute to the slowed relaxation rate of the left ventricle (LV) in patients with coronary artery disease (CADpts). Simultaneous observations were made on the time constant (Tc) of the isovolumic pressure decay and left ventriculography at the control period and after right atrial pacing. Subsequently, the subjects investigated were divided into 3 groups, i.e. normal subjects (Group I, n = 8), CADpts with normal wall motion during the control period (Group II, n = 21), and CADpts with RWMA during the control period (Group III, n = 28). The latter two groups were further divided into two subgroups according to the presence (Group IIa and IIIa) or absence (Group IIb and IIIb) of pacing-induced RWMA. We measured Tc by a method of exponential analysis that could estimate the asymptote.

During the control period, Tc was significantly prolonged in Group III (82 ± 26 msec) than that in Group I (60 ± 6 msec) and Group II (63 ± 12 msec). Tc was prolonged in proportion to the extent of RWMA during the control period. Immediately after right atrial pacing, Tc was markedly prolonged in Group IIa (from 61 ± 12 to 90 ± 20 msec, p < 0.001) and in Group IIIa (from 73 ± 26 to 95 ± 34 msec, p < 0.001). The post-pacing prolongation of Tc was closely correlated with the extent of post-pacing RWMA. From these results, it is postulated that RWMA may play an important role as a causes of the altered LV relaxation in CADpts.

CARDIAC muscle relaxation is a complex, energy dependent process. Animal data show that the relaxation is impaired under the condition of myocardial ischemia in isolated cardiac muscle as well as in anesthetized and conscious animals. In patients with coronary artery disease (CAD), the rate of left ventricular (LV) relaxation estimated by peak negative dp/dt decreases during myocardial ischemia. However, these findings are inconclusive because peak negative dp/dt is considerably influenced by heart rate (HR), systolic LV pressure (LVSP), end-systolic volume (ESV) and other factors. More recently the time constant of LV pressure decay during isovolumic relaxation has been shown to be relatively independent of other determinants of cardiac performance by Weiss et al. and has been proposed as an useful index to evaluate LV diastolic property.

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reported that the time constant was prolonged during pacing induced angina, although the mechanism of this prolongation remains unclear. It is well known that in patients with CAD LV function can be significantly impaired with marked alterations in the isovolumic and ejection phases of contraction.\textsuperscript{12}

On the other hand, despite current interest in the time constant for pressure decay in isovolumic relaxation, little attention has been paid to the relationship between the time constant and regional wall motion abnormality. We used the time constant of LV pressure decay during isovolumic relaxation as an index for assessing LV diastolic properties. Although time constant has been calculated as a negative reciprocal slope of a natural logarithm of pressure against time\textsuperscript{5,7,10} this conventional semilogarithmic method of estimating the time constant of exponential is valid only when the asymptote of the exponential is zero\textsuperscript{13} When the asymptote is negative, an upward shift of the pressure-time curve results in prolongation of traditional time constant, even though the pressure decay has not really changed. Therefore the traditional method is unreliable.

In this study, we estimated the time constant of isovolumic pressure decay during the period of LV isovolumic relaxation by a method of an exponential analysis that involved the estimation of the asymptote.\textsuperscript{13} We used these techniques for assessing LV relaxation in patients with CAD during the control period and post pacing state and studied the relationships among the rate of isovolumic relaxation and hemodynamic and angiographic findings of LV.

PATIENTS AND METHODS

Fifty-seven patients who were suspected of having CAD (mean age 54 years, range 39–65 years) were studied during diagnostic cardiac catheterization. The number of patients with CAD who had significant stenosis more than 75% in at least one coronary artery were 49. Eight patients with completely normal findings of coronary arteries and left ventriculography served as control. All patients were in sinus rhythm, and patients with hypertension or valvular heart disease were excluded from this study. All cardioactive drugs were discontinued for at least 24 hours before the commencement of the observation. Complete consent was obtained from each patient, and no unfavorable complication occurred as a result of this study.

Methods and Protocol

Cardiac catheterization was performed via the femoral approach in a fasting state and without premedication. LV pressure was recorded by a high fidelity micromanometer-tipped catheter (Millar Instruments). The micromanometer system was calibrated against a mercury manometer before insertion and again after withdrawal of the catheter. A bipolar electrode catheter was positioned in the high right atrium for pacing after collection of initial hemodynamic data. Left ventriculography was performed with single plane 35 mm cine angiography at 60 frames/sec in the right anterior oblique projection (Philips Poly-Diagnost C) using a 8Fr pigtail catheter. During the cineventriculographic study, high fidelity LV pressure and peak positive dp/dt were calculated with a computer system (Philips ACS). Control LV graphy with simultaneous measurement of LV pressure was initially performed. After LV pressure had returned to baseline, HR increased with atrial pacing by 20 beats/min every one minute until the ventricular rate of 140–160 beats/min was obtained. All patients maintained 1 : 1 A–V conduction. PACing was continued at this constant rate for 5 minutes or until typical angina pectoris developed, and then left ventriculography and the measurement of LV pressure were performed again during the first 10–15 beats after cessation of the right atrial pacing. Then, the coronary arteriography was performed in all patients by the Judkins technique.

![Fig.1. Segmental wall contraction of the normally contracting ventricle.](image-url)
TABLE I SUMMARY OF CLINICAL AND CATHETERIZATION DATA IN NORMAL SUBJECTS AND PATIENTS WITH CORONARY ARTERY DISEASE (CAD)

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects (Group I)</th>
<th>Patients with CAD and normal wall motion (Group II)</th>
<th>Patients with CAD and abnormal wall motion (Group III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient (No.)</td>
<td>8</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 8</td>
<td>56 ± 7</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>Sex</td>
<td>4M, 4F</td>
<td>19M, 2F</td>
<td>26M, 2F</td>
</tr>
<tr>
<td>Previous MI (No. of patients)</td>
<td></td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Inferior</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>0</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>CAD (No. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1V</td>
<td>0</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>2V</td>
<td>0</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>3V</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Values represent mean ± SD
Abbreviations: MI = myocardial infarction; V = coronary vessel with luminal stenosis more than 75%

TABLE II SUMMARY OF PRESSURE AND VOLUME DATA

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects Group I (n = 8)</th>
<th>Patients with CAD and normal wall motion Group II (n = 21)</th>
<th>Patients with CAD and subnormal wall motion Group III (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>62 ± 5</td>
<td>76 ± 18</td>
<td>73 ± 13</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>135 ± 368</td>
<td>138 ± 16</td>
<td>131 ± 25</td>
</tr>
<tr>
<td>LVSP/min (mmHg)</td>
<td>0.3 ± 0.7</td>
<td>1.3 ± 1.8</td>
<td>4.7 ± 4.2**</td>
</tr>
<tr>
<td>LVSP/dp/dt (mmHg/sec)</td>
<td>11 ± 3</td>
<td>13 ± 4</td>
<td>16 ± 5*</td>
</tr>
<tr>
<td>LVESV (ml/m²)</td>
<td>1585 ± 368</td>
<td>1793 ± 385</td>
<td>1568 ± 332</td>
</tr>
<tr>
<td>LVESV/VP (ml/m²)</td>
<td>22 ± 5</td>
<td>24 ± 8</td>
<td>54 ± 22**</td>
</tr>
<tr>
<td>Tc (msec)</td>
<td>72 ± 4</td>
<td>72 ± 7</td>
<td>50 ± 11**</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; LVSP = left ventricular systolic pressure; LVSPmin = left ventricular minimal pressure; LVEDP = left ventricular end-diastolic pressure; LV(+)/dp/dt = left ventricular peak positive dp/dt; LVESV = left ventricular end-diastolic volume; Tc = time constant of pressure decay
Values are mean ± SD
Group I vs Group III: *p < 0.05, **p < 0.001; Group II vs Group III: †p < 0.01, ††p < 0.005

Measurements and Computations

For evaluation of LV function, cine films were projected on a video camera, and the ventricular silhouettes were outlined with a light pen on a video screen. A computer system (Philips LVV 100) derived the correction factor for X ray magnification and calculated volumes by the area-length method. Both premature and post premature beats were excluded from the analysis. All the analyses were performed within the first three beats of the commencement of injection. The angiographic ejection fraction was calculated according to the standard formula. Volume data were corrected for the body surface area. Regional wall motion was examined by dividing LV silhouette into eight segments. The long axis extended from the midpoint of aortic orifice to the apex, and three vertical lines to the long axis at quarter-length intervals divided the LV silhouette into eight segments, as shown in Fig. 1. The segmental wall contraction (SWC) was calculated as follows:

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Statistical Analysis

One way analysis of variance was performed to determine the presence of significant differences between the various groups. If the analysis of variance was significant, p values were obtained by the unpaired Student's t-test. The paired data before and after pacing were compared using the paired Student's t-test. Values were expressed as mean ± SD and p < 0.05 was considered significant.

RESULTS

(1) Comparison among groups during control period (Table I and II). The 57 patients were divided into three groups according to their coronary arteriography and LV graphy during the control period.

Group I consisted of 8 normal subjects (4 males and 4 females) with normal coronary arteries and LV function. Group II consisted of 21 patients (19 males and 2 females) with CAD and normal regional wall motion. Four patients had electrocardiographic evidence of previous myocardial infarction. Group III consisted of 28 patients (26 males and 2 females) with CAD and regional wall motion abnormality at control period. All the patients in this group had electrocardiographic evidence of previous transmural infarction at least 6 weeks before the study. The details of the three groups are listed in Table I.

Table II summarizes the results of the hemodynamic data in each group obtained during control period. In terms of LV function, the subjects in Group I had good LV function, and patients in Group II did not differ significantly from those in Group I, although HR, Tc and LV minimal diastolic pressure (LVPmin) were higher. Basal HR and LVSP, showed almost the same values in Group I, II and III. However, compared with Group I and Group II, the patients in Group III had significantly higher values in LVEDP (16 ± 5 mmHg in Group III, 13 ± 4 mmHg in Group II and 11 ± 3 mmHg in Group I), and LVEDV (106 ± 28 ml/m² in Group III, 82 ± 19 ml/m² in Group II and 85 ± 10 ml/m² in Group I). On the other hand, the ejection fraction (LVEF) was significantly lower in Group III than Group II and Group I (50 ± 11% in Group III, 72 ± 7% Group II and 72 ± 4% in Group III). Tc in Group III (82 ± 26 msec) was significantly longer than that of Group I (60 ± 6 msec) and Group II (62 ± 12 msec),

Estimation of Time Constant

The index of LV relaxation, time constant (Tc), was calculated with a microcomputer (SANYO MBC 2) from the point of peak negative dp/dt to the time at which pressure decreased to the level of LV end-diastolic pressure (LVEDP) of the preceeding beat. Tc was derived from an exponential curve fitting. Thus P(t) = ae^{bt} + c, where P(t): pressure at time t, t: time in msec after peak negative dp/dt, and c: the asymptote. Tc = -1/b.
although there were no significant differences between Group I and II.

(2) The relation of Tc to regional wall motion abnormality during the control period (Fig. 2).

The patients with CAD were divided into 4 classes according to the number of abnormally contracting segments, i.e. none (n = 21, without wall motion abnormality), mild (n = 10, with wall motion abnormality in one or two segments), moderate (n = 10, with that in three or four segments), and severe (n = 8, with that in five or six segments). Figure 2 illustrates Tc in these four classes, namely 63 ± 12 msec, 71 ± 25 msec and 103 ± 23 msec, respectively. Tc was prolonged in proportion to the extent of regional wall motion abnormality during control period. In contrast, there were no significant relationship between Tc and the severity and the extent of diseased coronary artery.

(3) Comparisons of each hemodynamic parameter between the control period and the period immediately after the atrial pacing in five groups, i.e. Group I, IIa, IIb, IIIa, IIIb (Table III and Fig. 3).

Groups II and III were divided into two subgroups according to the presence (Group IIa and IIIa) or absence (Group IIb and IIIb) of pacing-induced regional wall motion abnormality which was identified by cineangiographic findings. In Group I atrial pacing was performed for five minutes in each patient without development of chest pain. LVFlow, LVEDP, LVSP, LV peak positive dp/dt, end-diastolic volume (EDV), ESV and EF after the right atrial pacing were not significantly different from those during the control period. The findings of left ventriculography remained normal after the pacing without the development of regional wall motion abnormality and in addition Tc remained unchanged.

In the patients in Group IIa who indicated pacing-induced regional wall motion abnormality on the post pacing ventriculography, HR, LVSP and LV peak positive dp/dt were unchanged. LVFlow, LVEDP, LVESV and LVEF increased significantly, whereas LVEF decreased significantly. In addition, Tc was markedly prolonged (61 ± 12 msec vs 90 ± 20 msec, p < 0.001). In the patients in Group IIb, who showed no development of new regional wall motion abnormality after the pacing, all hemodynamic parameters were unchanged. In patients in Group IIIa who showed worsening of their regional wall motion abnormality on post pacing ventriculography,
Fig. 3. Pacing-induced changes in time constant (Tc) in each group. C: control period, PP: post-pacing period.

Fig. 4. Pacing-induced changes in time constant (Tc) in patients with none (n = 28), mild (n = 11) and severe (n = 10) pacing-induced regional wall motion abnormality. The bars represent group mean ± SE.

LVEDP, LVPmin, LVESV and RVSP increased. LVEF decreased significantly, while HR, LVSP, LV peak positive dp/dt and LVEDV were unchanged. On the other hand, Tc was significantly prolonged (73 ± 26 msec vs 95 ± 34 msec, p < 0.001). In patients with Group III b without pacing-induced regional wall motion abnormality, LVEF, LVSP, LVEDV, LVESV and LV peak positive dp/dt were unchanged, although LVPmin and LVEDP increased significantly. Tc was also unchanged (89 ± 26 msec vs 89 ± 28 msec).

(4) Relation between pacing-induced changes in Tc and regional wall motion abnormality (Fig. 4).

All the patients with CAD were divided according to the number of segments which developed or worsened their regional wall motion abnormality on post pacing ventriculography; none (n = 28, without pacing-induced regional wall motion abnormality), mild (n = 11, with regional wall motion abnormality in one or two segments), and severe (n = 10, with that in three or four segments). Figure 4 illustrates pacing-induced changes in Tc in patients with none, mild, severe pacing-induced regional wall motion abnormality. In those three groups, changes in Tc were 0.5 ± 17 msec, 20 ± 10 msec and 36 ± 7 msec, respectively. Tc was prolonged in proportion to the changes of the severity of pacing-induced regional wall motion abnormality. On the contrary, there was no significant relationship between the changes in Tc and those in other hemodynamic parameters.
DISCUSSION

Clinical and experimental studies have shown that changes in cardiac performance during isovolumic LV relaxation can be a sensitive indicator of myocardial dysfunctions, and the study of the relaxation phase in patients with CAD has been considered to be of special importance for assessing their LV function.

We used the time constant of LV pressure decay during isovolumic relaxation as an index for assessing LV diastolic properties. Weiss et al. and Fredriksen et al. have shown in dogs that isovolumic pressure decay after peak negative dp/dt was monoexponential for at least 100 msec and could be characterized by the time constant T of an exponential, and that the time constant T was unaffected by changes in the LVSP or LVEDP, stroke volume or velocity of shortening but decreased with positive inotropic interventions. Taw et al. have suggested that the time constant was prolonged during myocardial ischemia. Mann et al. reported a similar conclusion; i.e. relaxation abnormalities occurred during an attack of angina pectoris induced by atrial pacing, and a higher time constant of LV pressure decay than in resting conditions was demonstrated. In these previous studies, the time constant has been calculated as a negative reciprocal slope of the natural logarithm of pressure against time. This semi-logarithmic method of estimating the time constant of an exponential is valid only when the asymptote of the exponential is zero. When the asymptote is negative, an upward shift of the pressure time course results in prolongation of the time constant even though the rate of LV relaxation has not really changed. In other words, the increase in the time constant observed during these experiments may be due to an increase in LVEDP during ischemia. Therefore, in this study we computed the time constant Tc by an exponential analysis method that estimates the asymptote.

Our study demonstrated that Tc was prolonged in patients with CAD and regional wall motion abnormality. Tc was prolonged in proportion to the severity of wall motion abnormality. Further, our data indicated that Tc was prolonged after right atrial pacing in patients with pacing-induced regional wall motion abnormality, and its value was closely related to the severity of pacing-induced regional wall motion abnormality.

The mechanisms responsible for the prolongation of Tc during the control period and the post-pacing period in patients with CAD could not be clarified in our study. Papapietro et al. have reported similar results, indicating that the rate of LV relaxation by peak negative dp/dt was impaired under basal conditions in patients with CAD and abnormally contracting segments. They suggested that dyssynchronous wall motion in the ischemic area during isovolumic relaxation, as hypothesized by Water et al., impairs LV relaxation. Recently, Kumada et al. have reported in conscious dog that such dyssynchronous wall motion between the ischemic and the normal zone can greatly modify the rate of LV pressure decay. Therefore, an increase in Tc values which was observed in patients with CAD during the control period and the post-pacing period is consistent with the dissociation of the contraction-relaxation sequence, i.e. dyssynchronous wall motion. It is, thus, suggested that the characteristic changes in Tc is of diagnostic value for CAD, because an increase in Tc at rest or after right atrial pacing in patients with CAD is closely related to the presence or absence of regional wall motion abnormality.

It is postulated that regional wall motion abnormality may play an important role as one of the causes to alter LV relaxation in patients with CAD.

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