EFFECTS OF LEFT VENTRICULAR DYSFUNCTION ON LEFT ATRIAL PERFORMANCE IN PREVIOUS MYOCARDIAL INFARCTION AND DURING PACING-INDUCED MYOCARDIAL ISCHEMIA IN ANGINA PECTORIS

Tohru Yamasaki, M.D., Motoshi Takeuchi, M.D., Kazuhiro Fujitani, M.D.* and Hisashi Fukuzaki, M.D.

This study aimed to evaluate acute and chronic response of left atrial function to left ventricular dysfunction in patients with coronary artery disease. We studied simultaneous measurements of left atrial volume by biplane cineangiography and left ventricular pressure at rest and after pacing in 59 patients with coronary artery disease and 11 normal subjects. At rest, 35 patients with previous myocardial infarction (MI group) had low left ventricular filling rate of the first third in diastolic time, large left atrial volume before contraction (LA pre-ACV) and large left atrial ejection volume (LAEV), compared with control group. Left atrial ejection fraction (LA EF), the ratio of LAEV to LA pre-ACV, was similar between both groups. LAEF was maintained within a wide range of values in accordance with left ventricular peak A pressure, except for 3 patients who had high values of left ventricular peak A pressure and low values of LAEF. After a right atrial pacing stress test, time constant was prolonged and mean emptying rate of left atrial volume during early diastole decreased in 11 patients with angina pectoris who had an increase greater than 5 mmHg in left ventricular end-diastolic pressure after pacing. In these group, LA pre-ACV increased, LAEF decreased and LAEV was unchanged. These results suggest that left atrial performance responds differently to acute and chronic left ventricular dysfunction in patients with coronary artery disease.

In coronary artery disease, abnormalities of left ventricular (LV) early diastolic filling have been described at rest and during myocardial ischemia, which may result from impaired LV relaxation and compliance.1–5 During late diastole, left atrial (LA) contraction has been considered to play an important role in maintaining LV filling.6–8 In canine atrial muscle, LA performance is affected by loading conditions as well as LV, and LA function interacts with LV function during diastole of LV.9 In man, the relation between LA performance and LV dysfunction has not been previously reported.

This study was designed to evaluate acute and chronic response of LA function to LV dysfunction in patients with coronary artery disease with reference to atrioventricular interaction. We studied simultaneous measurements of LA volumes and LV pressure at rest in patients with previous myocardial infarction and during pacing-induced ischemia in patients with angina pectoris.

Key words: Left atrial function Left ventricular dysfunction Diastole

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Left Atrial Function in Coronary Artery Disease

TABLE I CLINICAL DATA AND LEFT VENTRICULAR VOLUME INDICES IN STUDY 1

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>MI group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Age (years old)</td>
<td>59 ± 13</td>
<td>58 ± 10</td>
</tr>
<tr>
<td>Sex</td>
<td>male</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>2</td>
</tr>
<tr>
<td>No. of diseased vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vessel</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>2 vessel</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>3 vessel</td>
<td>-</td>
<td>13</td>
</tr>
</tbody>
</table>
| LVEDVI (ml/m³)   | 88 ± 11       | 114 ± 33*
| LVESVI (ml/m³)   | 27 ± 4        | 58 ± 30#
| EF (%)           | 69 ± 5        | 51 ± 12##
| Early Filling Rate (ml/sec.m⁻²) | 221 ± 76 | 157 ± 50#
| Filling Time (msec) | 448 ± 121 | 494 ± 145

* p < 0.05, # p < 0.005, ## p < 0.001 vs control. MI = myocardial infarction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; EF = ejection fraction; Values are mean ± SD.

METHODS

Study Patients (Tables I and II)

This study consisted of 2 protocols. In the first protocol, 46 patients with suspected coronary artery disease were studied during diagnostic cardiac catheterization. All patients were in sinus rhythm and had a normal PQ interval on electrocardiogram. Thirty-five patients had previous myocardial infarction (24 with anterior, 9 with inferior and 2 with antero-inferior myocardial infarction) with typical histories and abnormalities of electrocardiogram, left ventriculography and myocardial scintigraphy (MI group). In this group all patients had significant stenosis (greater than 75% diameter narrowing) in at least one coronary artery. Eleven subjects who had a history of atypical chest pain but completely normal findings for the coronary arteriogram and left ventriculogram served as controls.

In the second protocol, 24 patients with a typical history of stable effort angina pectoris had significant stenosis in coronary artery. Fourteen of them had previous myocardial infarction (12 with anterior and 2 with inferior myocardial infarction). All patients were in sinus rhythm and had a normal PQ interval on electrocardiogram. None of the patients had a significant stenosis in the proximal portion of circumflex artery and mitral regurgitation. Patients with valvular heart disease, hypertension, unstable angina pectoris and congestive heart failure were excluded from this study. This study was performed at least 72 hours after cessation of treatment with beta-adrenergic blocking agents or calcium channel blockers and at least 12 hours after cessation of nitroglycerin therapy. Complete informed written consent was obtained from each patient and no unfavourable complication occurred in this study.

Study protocol 1

Cardiac catheterization was performed using the femoral approach with patients in a fasting state and without premedication. LV pressure was recorded by a high fidelity micromanometer-tipped catheter (7F Millar, PC 370 or 8F, PC 484A). The transducers were immersed in a 37°C water bath for 1 hour, balanced and electronically calibrated against a mercury manometer in the bath immediately before insertion and after

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### Table III: Hemodynamic Data of Left Ventricle and Left Atrium in Patients With Previous Myocardial Infarction and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Left Ventricular Pressure</th>
<th>Left Atrial Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (bpm)</td>
<td>LVSP (mmHg)</td>
</tr>
<tr>
<td>Control group</td>
<td>66 ± 11</td>
<td>144 ± 23</td>
</tr>
<tr>
<td>MI group</td>
<td>63 ± 10</td>
<td>135 ± 25</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, #p < 0.005, ##p < 0.001 vs control. Values are mean ± SD. HR = heart rate; LVSP = left ventricular systolic pressure; LVPmin = left ventricular minimal pressure; LVEDP = left ventricular end-diastolic pressure; LVP peakA = left ventricular pressure of peak A wave; T = time constant of left ventricular pressure decay; Pre-ACV = atrial pre-contraction volume; Post-ACV = atrial post-contraction volume; LAEV = left atrial ejection volume; LAEF = left atrial ejection fraction.

withdrawal of the catheter. During the catheterization, the transducers were checked for baseline drift by comparison with a Statham P23ID transducer connected with the fluid-filled catheter in LV. When necessary, we rebalanced the Millar transducer by removing the catheter through the femoral artery with a catheter introducer during the study. Left ventriculography was performed with biplane 35 mm cineangiography in the right anterior oblique (30°) and left anterior oblique (60°) projections. A bolus 30 ml of iopamidol (Iopamiron) was injected via the 8F pigtail catheter at a rate of 12 ml/sec, with cinefilm exposed at 60 frames/sec. Thirteen minutes later, after the hemodynamic parameters were returned to baseline, an 8F Berman angiographic catheter was positioned in the trunk of the pulmonary artery and a bolus 40 ml of contrast materials was injected into the pulmonary artery at a rate of 15 ml/sec with biplane cineangiography in the anterior and lateral projections. During the angiographic study, high fidelity LV pressure was recorded during breath holding at mid-inspiration. LV pressure and the time of the peak R wave on the electrocardiogram were also sampled synchronously with frame exposure, and displayed in digital form on the corresponding cineframe (Cine data, Philips). Coronary arteriography was then performed in all patients using the Judkins technique. After the catheterization, the grid was placed at the level of LV and LA for X-ray magnification and distortion.

**Study protocol 2**

After the left ventriculography and the left atriography at rest as described in the first protocol, a pacing stress test was performed. After the hemodynamic values returned to the baseline, a bipolar electrode catheter was positioned in the high right atrium for pacing. While all patients were maintaining 1:1 AV conduction, the heart rate was incrementally increased with atrial pacing by 20 beats/min every minute until atrioventricular rate of 140–160 beats/min was obtained. Pacing was continued at this rate for 5 min or until typical angina pectoris of moderate severity developed, at which time the pacing was abruptly discontinued. Repeated left atriography and the simultaneous measurements of LV pressure were performed during the first 5–10 beats in a stable sinus rhythm while recording the electrocardiogram in leads II, V₃ and V₅.

**Left ventricular and left atrial volume measurements**

For the evaluation of LV function, cinefilms were projected into a videocamera and ventricular silhouettes were outlined with a light pen on a videoscreen. A computer system (Philips LVV 100) calculated volumes by applying Simpson’s rule. Patients with both premature and post premature beats during and after left ventriculogram were excluded from this study. All the analyses were performed within the first 3 beats of the commencement of injection. The angiographic ejection fraction was calculated according to the standard formula.

Ventricular filling was quantified with frame-by-frame angiographic volumes from mitral valve opening to end-diastole. The time of end-diastole was defined as the beginning of the rapid rise in

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LV pressure immediately after the onset of the QRS complex. The time from mitral valve opening to end-diastole was referred to as the LV filling time. This filling time was divided into 3 equal intervals. The mean filling rate of the first interval was termed early filling rate$^5$. 

For evaluation of LA function, LA silhouettes in earliest beat which showed satisfactory opacification of LA chamber in both the anterior and lateral projections were outlined on a videoscreen and LA volumes were obtained by the area-length method, as previously described$^{11}$. LA volume curve was obtained with frame-by-frame angiographic volumes during one cardiac cycle. A 3 point moving average filter was applied. LA volume before atrial contraction, minimal volume and the difference between these volumes were termed pre-atrial contraction volume, post-atrial contraction volume and ejection volume, respectively. The left atrial ejection fraction (LAEF) was calculated by the ratio of ejection volume to pre-atrial contraction volume, as an index of LA pump function. After mitral valve opening, that LA empties rapidly is responsible for rapid filling of LA.$^{12}$ We calculated mean rate of LA volume during the time from mitral valve opening to the end of passive atrial emptying (passive atrial emptying time) and this rate was termed passive atrial emptying rate, as an index of LV rapid filling.

**Pressure analysis**

LV pressure was computed and verified by recording at a paper speed of 250 mm/sec. The index of LV relaxation, time constant, was calculated with a microcomputer (SANYO MBC 220) from the point of peak negative dp/dt to the time at which pressure decreased to the level of LV end-diastolic pressure of the preceding beat$^{13}$. Time constant was derived from an exponential curve fitting with a variable asymptote, as previously reported$^{5,14,15}$. Thus, $P(t) = ae^{bt} + c$, where $a$ = constant, $e$ = the base of natural logarithm, $P(t)$ = pressure at time, $t$ = time after peak negative dp/dt, $c$ = asymptote and time constant ($T$) = $-1/b$, where $b$ = constant.

**Statistical analysis**

Linear regression analysis of paired data was performed according to standard methods. The
difference between the control patients and those with myocardial infarction was tested by the unpaired t test and the differences between two stages in a given of patients were tested by the paired t test. A p value < 0.05 was considered significant. All data were expressed as the mean ± SD.

RESULTS

Study 1

*hemodynamic data of left ventricle in study 1* (Tables I and III)

All hemodynamic parameters of study 1 are listed in Tables I and III. No significant difference in heart rate or LV systolic pressure between the MI and the control groups was observed. In the MI group, LV end-diastolic pressure, minimal pressure and peak value of A wave in LV (peak A pressure) were significantly elevated than the control group. Time constant was significantly more prolonged in the MI group than the control group. In the MI group, both LV end-diastolic volume index and LV end-systolic volume index were significantly larger and LV ejection fraction was significantly decreased compared with the control group. LV early filling rate was also decreased significantly in the MI group. Filling time was not different between the two groups.

*hemodynamic data of left atrium in study 1* (Table III)

Pre-atrial contraction volume was larger in the MI group than the control group. Post-atrial contraction volume was not different between the two groups. Ejection volume was significantly larger in the MI group than in the control group. However, LAEF was not different between two groups.

*atrioventricular interaction in study 1* (Figs. 1, 2 and 3)

Interaction between LA and LV is shown in Figs. 1, 2 and 3. A significant correlation between LV early filling rate and pre-atrial contraction volume was observed ($r = -0.58$, $p < 0.001$; Fig. 1). In all subjects, LA ejection volume was poorly, but significantly, related to pre-atrial contraction volume ($r = 0.46$, $p < 0.01$, Fig. 2). In MI group, except 3 patients who had low values in LA ejection volume with large pre-atrial contraction volume, a good correlation was observed between these patients ($r = 0.71$, $p < 0.001$). Fig. 3 shows the relation between LAEF and LV peak A pressure. LAEF was inversely correlated with LV peak A pressure ($r = -0.64$,

<p>| TABLE IV HEMODYNAMIC DATA OF LEFT VENTRICLE AND LEFT ATRIUM IN CONTROL AND POST-PACING BEAT |
|---------------------------------|---------------------------------|----------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Left Atrial Volume</th>
<th>Post-ACV</th>
<th>LAEF</th>
<th>PAEF</th>
<th>Post-PAEF</th>
<th>PACI</th>
<th>PACI</th>
</tr>
</thead>
<tbody>
<tr>
<td>m/min</td>
<td>mmHg</td>
<td>mm/min</td>
<td>mmHg</td>
<td>%</td>
<td>mm/min</td>
<td>mm/min</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>------</td>
<td>------</td>
<td>----------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Group A control</td>
<td>66</td>
<td>136</td>
<td>6</td>
<td>38</td>
<td>6</td>
<td>1.3</td>
</tr>
<tr>
<td>post pacing</td>
<td>± 8</td>
<td>± 3</td>
<td>± 2</td>
<td>± 2</td>
<td>± 2</td>
<td>± 2</td>
</tr>
<tr>
<td>Group B control</td>
<td>71</td>
<td>150</td>
<td>6</td>
<td>49</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>post pacing</td>
<td>± 8</td>
<td>± 3</td>
<td>± 2</td>
<td>± 2</td>
<td>± 2</td>
<td>± 2</td>
</tr>
</tbody>
</table>

* $p<0.01$, $\# p<0.001$, $\# # p<0.005$ vs control. Values are mean ± SD. Group A: After pacing fall or less than 5 min, increase in LV end-diastolic pressure, minimal pressure and peak value of A wave in LV (peak A pressure) were significantly elevated than the control group. Time constant was significantly more prolonged in the MI group than the control group. In the MI group, both LV end-diastolic volume index and LV end-systolic volume index were significantly larger and LV ejection fraction was significantly decreased compared with the control group. LV early filling rate was also decreased significantly in the MI group. Filling time was not different between the two groups.
p < 0.001). But except for 3 patients who had high values of LV peak A pressure (27, 28 and 30 mmHg) with low values of LAEF, LAEF was maintained within a wide range of values in LV peak A pressure. These 3 patients corresponded to the patients who had low values in LA ejection volume for pre-atrial contraction volume in Fig. 2.

Study 2

In study 2, we separated our patients into two groups. After pacing 13 patients had a fall or an increase less than 5 mmHg in LV end-diastolic pressure as compared with the baseline (Group A). Eleven patients had an increase greater than 5 mmHg in LV end-diastolic pressure after pacing (Group B). In group B, 10 patients (91%) had typical angina with moderate severity or more and 9 patients (82%) showed ischemic ST depression (1 mm or greater ST segment depression) on electrocardiogram during and immediately after pacing. In contrast, in the group A, 4 patients (31%) had angina and 3 patients (23%) showed ischemic ST depression.

Baseline LV end-diastolic volume index, end-systolic volume index or ejection fraction were not different between the two groups (Table II).

Hemodynamic data of the left atrium in study 2 (Table IV)

Table IV summarizes control and post-pacing hemodynamic data for patients in groups A and B. Heart rate and LV systolic pressure were unchanged in the control and post-pacing beat in groups A and B. In group A, LV minimal pressure, LV end-diastolic pressure and LV peak A pressure were unchanged after pacing. In group B, LV minimal pressure, LV end-diastolic pressure and LV peak A pressure were significantly increased in the post-pacing beat. Time constant was also prolonged significantly in group B.

Hemodynamic data of the left atrium in study 2 (Table IV, Figs. 4 and 5)

In the post pacing beat, passive atrial emptying rate decreased in group B, but was maintained in group A. Passive atrial emptying time was unchanged in both groups. Pre-atrial contraction volume increased significantly in groups A and B. Post-atrial contraction volume increased in group B, but was unchanged in group A. LA ejection volume increased in group A, but was unchanged in group B. In group A, LAEF increased in the post-pacing beat, in contrast, in group B LAEF decreased. Fig. 4 shows the correlation between the changes in pre-atrial contraction volume and LA ejection volume. In all patients, there was a significant correlation between the two parameters (r = 0.51, p < 0.02). Furthermore, the correlation coefficient increased to 0.85 when comparison was limited to group A (p < 0.001). The change of LAEF was inversely correlation with the change of LV peak A pressure (r = -0.76, p < 0.001, Fig. 5).

DISCUSSION

Although filling abnormalities of LV in coronary artery disease have been recently investigated,1-3,5 few clinical data are available con-

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cerning atrioventricular interaction between LA and LV during diastole. Measuring LA volume by cine angiography, we evaluated the effects of LV dysfunction on LA performance in patients with previous myocardial infarction and during myocardial ischemia in coronary artery disease.

In study 1, LV early filling rate was decreased in patients with previous myocardial infarction compared with normal subjects. Pre-contraction volume of LA was larger than the normal subjects and inversely correlated with early filling rate of LA. Ejection volume of LA in previous myocardial infarction was increased compared with the normal subjects and correlated with pre-ejection volume of LA. These findings suggested that in previous myocardial infarction increased preload of LA caused by impairment of LA early filling could augment atrial contribution to LV, resulting in maintenance of LA stroke volume.

After the onset of ventricular filling, the blood available for rapid filling of the ventricle in early diastole is obtained primarily from the atrium. Our data suggests that in the presence of LV early diastolic impairment, the amount of blood filled from atrium to ventricle during early diastole is decreased. As a result, pre-contraction volume of LA, preload to LA, may be increased.

As observed in experimental preparations, atrial muscle was also operated through Frank-Starling mechanism, as well as LV. Braunwald noted the effect of atrial systole on the relationship between LV end diastolic pressure and mean LA pressure. Matsuda et al showed similar results through the pressure-volume study of LA in previous myocardial infarction. In our study, LA ejection volume was increased in proportion to pre-contraction volume of LA, suggesting that an increase in preload of LA augments stroke volume of LA in previous myocardial infarction.

In the present study, LA ejection fraction, which was used as an index of LA systolic performance, in previous myocardial infarction was similar to that in normal subjects. The relationship between LA ejection fraction and LV peak A pressure showed that LA ejection fraction in previous myocardial infarction was maintained over a wide range of LA peak A pressure as a measure of afterload to LV (Fig. 3). However, LA ejection fraction was decreased in 3 patients when LV peak A pressure was extremely high. Experimental studies have shown that an increase in pressure by atrial contraction produced little increase in segment length of LV when the ventricle was on the steep portion of the pressure-length curve and ventricular end-diastolic pressure was elevated. Previous work showed that LV could compensate systolic performance for an increase in pressure by an increase in ventricular end-diastolic volume and that when the limit of preload reserve was reached, systolic performance was sensitive to the change in afterload, i.e., afterload mismatch. Performance of atrial muscle is also known to be depressed by increase in afterload as well as LV. Thus, LA systolic performance in previous myocardial infarction might be maintained over a wide range of afterload. However, when afterload to LA was too high, systolic performance of LA might reduce.

During acute myocardial ischemia in coronary artery disease, altered diastolic properties are important factors in producing the elevated filling pressures. To evaluate left atrial function on acute impairment of diastolic function, we divided our patients in the pacing study into 2 groups according to the degree of the elevation in LV end-diastolic pressure in post-pacing beat.

In study 2, in the group B patients who had significant elevation in LA end-diastolic pressure and prolongation of time constant, passive atrial emptying rate became decreased, reflecting the impairment of LV rapid filling. In response to filling abnormalities of LA, pre-atrial contraction volume increased, but LA ejection volume did not augment in group B. In addition, the changes in LA ejection fraction were related to the increase in LA peak A pressure from pre-pacing to post-pacing. These results suggest that during acute myocardial ischemia of LA, despite augmentation of LA preload caused by impairment of LA early filling, LA ejection volume might not increase and LA systolic performance might be reduced by an abrupt increase in LA diastolic pressure, afterload to LA, immediately after cessation of atrial pacing. Patients in group A who had a slight elevation or decrease in LA end-diastolic pressure during post-pacing periods had increased in LA ejection volume, pre-atrial ejection volume and LA ejection fraction. The changes in LA ejection volume were correlated with the changes in LA pre-contraction volume. The increase in LA ejection volume can be explained by the use of increased preload without the effect of afterload to LA.

We used passive LA emptying rate during LV early filling periods as an index of LV early filling. Abnormalities of LA passive emptying during LV early filling periods were observed in

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hypertensive heart disease and were sensitive indicators of impairments in LV early filling. There are a few limitations in this study. First, we did not calculate wall stress of LA. LA pressure was difficult to obtain in the clinical setting. In addition, LA has a very thin wall. Therefore, we evaluated LV peak A wave as an index of afterload to LA. Second, a reverse flow from LA to pulmonary vein during atrial systole might occur. However, studies of pulmonary venous flow using pulsed Doppler echocardiography showed that during atrial contraction, the flow from the pulmonary veins into the LA was either very slow or did not occur at all and no regurgitant flow from the atrium into the pulmonary veins was observed during LA systole. Finally, myocardial ischemia may induce papillary muscle dysfunction and mitral regurgitation may occur. When moderate mitral regurgitation occurs, LV early filling increases and LA systolic shortening also increases. However, it seems unlikely in this study.

In LV failure, atrial contribution is important in augmenting LV volume and pressure at end-diastole and improving LV performance. However, high elevation of LV diastolic pressure diminishes LA systolic preformance and subsequently LV performance may not be improved.

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