EFFECTS OF PRELOAD ALTERATION ON THE DEGREE OF ISCHEMIA AND FUNCTION OF ISCHEMIC MYOCARDIUM UNDER CONSTANT MEAN AORTIC PRESSURE, CORONARY PERFUSION PRESSURE AND HEART RATE IN ISOLATED PERFUSED CANINE HEART

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We examined the effects of preload alteration on global and regional (i.e., non-ischemic and ischemic areas) function in the presence of regional myocardial ischemia and on the degree of ischemia using 18 isolated, metabolically supported canine left ventricles. For this purpose, cardiac output (CO), systolic segment length change (SL), myocardial CO₂ tension (PmCO₂) and ST level of epicardial ECG were measured at 3 levels of left ventricular end-diastolic pressure (LVEDP), i.e., approximately 7 (low LVEDP), 11 (middle LVEDP), and 16 mmHg (high LVEDP) without and with left circumflex artery (LCx) stenosis under a constant mean aortic pressure (90 mmHg), mean coronary perfusion pressure (90 mmHg) and heart rate.

In the Pre-ischemic stage, CO and SL increased significantly when LVEDP was elevated in a stepwise fashion by changing the height of the reservoir connected to the left atrium. There were no significant changes in PmCO₂ or ST level. On the other hand, with LCx stenosis, CO did not show a subsequent increase at higher LVEDPs (i.e., from 796 ± 103 ml/min at middle LVEDP to 931 ± 153 ml/min at high LVEDP). Furthermore, there was no significant SL response in the LCx area following alterations of LVEDP, although there was considerable lengthening of end-diastolic length. Both increased PmCO₂ and ST level of the LCx area, following LCx stenosis, further increased significantly with elevation of LVEDP.

These results suggest the possibility that considerable elevation of LVEDP worsens the degree of ischemia and does not significantly augment ischemic regional myocardial function or global function, while mild elevation of preload improves or tends to improve simultaneously regional ischemic and global functions without aggravating the ischemic injury significantly. Therefore, we conclude that the preload level is quite important in managing ischemia induced myocardial dysfunction.

Key Words:
Cardiac function curve
Regional myocardial function
Myocardial CO₂ tension
Vasodilator therapy

ALTHOUGH there are many studies which have reported the effects of increasing 1–8 and decreasing 9–13 the preload on the function of ischemic hearts, we have little understanding of

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the direct effect of preload itself on not only the left ventricular function in ischemia, but also on ischemic regional function. One reason for this is that preload alteration is ordinarily combined with the afterload change, and the afterload change influences the coronary hemodynamics. Thus, if autoregulation of coronary circulation is already lost, for example by the presence of a severe coronary artery stenosis, it is possible for a change in coronary perfusion pressure to alter the coronary blood supply, and then the contractile state. Accordingly, these linked reactions have hindered analysis of the effects of preload alteration alone. Also, for the same reason, nitrite or other vasodilator agents are not suitable for analytically determining the effects of preload change.

Therefore, the purpose of this study was to assess the effect of preload change on myocardial ischemia under specifically-controlled hemo-

dynamic conditions using isolated metabolically supported canine left ventricles under a constant mean coronary perfusion pressure equal to the constant mean aortic pressure, and constant heart rate.

METHODS

1) Preparation (Fig. 1)

The experiments were performed using 18 isolated, metabolically supported left ventricles of mongrel dogs. The details of a similar experimental system are reported elsewhere14–17. The dogs (body weight 14.7–18.0 kg) were anesthetized intravenously with alpha-chloralose (50 mg/kg) and urethane (500 mg/kg). After a bilateral thoracotomy, a modified Gregg’s glass cannula was inserted and placed just above the aortic valve through the brachiocephalic artery. The heart was removed soon after ligation of the
annexing vessels under electrically induced ventricular fibrillation and with retrograde coronary perfusion of arterial blood from a support dog (body weight more than 20 kg) which was also anesthetized with alpha-chloralose and urethane. The glass cannula was manipulated into the main left coronary artery and fixed tightly there. The right atrium and the right ventricular free wall were cut off just after the ligation of the right coronary artery. The left circumflex artery (LCx) was perfused separately from the left main coronary artery with a hard tip polyvinyl catheter which was inserted into the proximal portion of the LCx artery. The catheter was carefully designed to have resistance equivalent to the modified Gregg's cannula which has a 4 mmHg pressure drop at a flow rate of 100 ml/min.

The coronary perfusion system consisted of a peristaltic pump (Harvard pump type 1215), filter (Marusho Pallfilter), air buffer and heat exchanger (37.0 ± 0.5°C). The end of the afferent limb of this perfusion system was divided into two tubes: one was connected to the modified Gregg's cannula and the other led to the LCx perfusion catheter. Venous blood gathered from the coronary veins was returned gravitationally to the bilateral femoral veins of the support dog through the filter and heat exchanger (37.0 ± 0.5°C). Blood coagulation was prevented with intravenous injection of heparin calcium (Eisai Co. LTD, 10000 U initially and 5000 U every one hour thereafter). The arterial blood gas of the support dog was measured frequently with a blood gas analyzer (Radiometer BMS 3 Mk 2, PHM 72 Mk 2) and blood pressure was monitored continuously. We tried to keep these parameters within their physiological ranges. Consequently the obtained values were as follows: PO₂; 69–108 mmHg (85 ± 12 mmHg, Mean ± SEM), PCO₂; 25–47 mmHg (34 ± 6 mmHg), pH; 7.33–7.55 (7.41 ± 0.06) and mean blood pressure: above 70 mmHg.

A glass cannula with large holes which was connected to the preload reservoir was inserted into the left atrium. The preload reservoir, which was made to overflow all the time, was filled with physiological saline pumped up from the heat exchange tank (37.0°C, 40 L). Thus, the height of the preload reservoir determined the left ventricular filling pressure. Left ventricular end-diastolic pressure (LVEDP) could be maintained at any given level by monitoring the amplified left ventricular pressure and regulating the height of the reservoir.

A hydraulic device which was made to be equivalent to the aortic input impedance of an adult dog was connected to the remaining aortic root, about 1.5 cm long. The details of this device have been described previously. Physiological saline was then ejected from the heart to the device and returned to the heat exchange tank. A portion of the modified Gregg's cannula was brought outside the device through the connecting part. Heart rate was kept constant with a bipolar pacing electrode tacked to the remnant right atrium (120–150, 138 ± 3 beats/min).

2) Measurements

Left ventricular pressure (LVP) was measured with a short stiff polyethylene tube that had been inserted through the apex and connected to a strain gauge pressure transducer (Toyo Sokki MPU 0.5). LVEDP was defined at the beginning of the upstroke of the pressure wave with reference to the R wave of ECG. Aortic pressure was obtained at the inlet of the hydraulic device with a short lateral tube. Mean left coronary perfusion pressure was also obtained at the proximal portion of the modified Gregg's cannula in the same way as LVP and aortic pressure. The characteristics of the measurement system have been described elsewhere. A common reference pressure of zero was set at the mid point of the left ventricle.

Instantaneous aortic flow was measured at the inlet of the device with an extracorporeal flow probe (12 mm I.D.) connected to a square wave electromagnetic flowmeter (Nihon Kohden MF 46). The mean value of aortic flow was obtained simultaneously by the electrical averaging method. Calibration was done by directly measuring the volume of fluid ejected per unit time. Mean total left coronary and LCx coronary flows were measured with a square wave electromagnetic flowmeter (3 mm I.D. Nihon Kohden MF 46).

Two pairs of miniature ultrasonic crystals (1.5–2.0 mm in diameter) were implanted in the subendocardium in the center of the left anterior descending artery (LAD) and LCx perfused areas, roughly parallel to the minor axis of the left ventricle. This segment length measurement system followed the design of Theroux et al. End-diastolic length (EDL) was defined at the LVEDP point and we obtained the systolic segment length change (SL) by measuring from EDL to the end-ejection point, which was defined by the aortic flow wave. Each measured value is presented as

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percent shortening of EDL. EDL is also presented as the percentage of that in the low LVEDP of the Pre-ischemic stage.

In 11 out of 18 dogs used for the present study, the myocardial carbon dioxide tension (PmCO₂) was measured with a catheter-tip ion sensitive field effect transistor (ISFET). The calibration of this system was performed using the warmed (37°C) physiological saline equilibrated by two different concentrations of CO₂ gas (5% and 10%), which had been previously measured with a gas analyzer (Radiometer BMS 3 Mk 2, PHM 72 Mk 2) as partial tension. The center of the ischemic area, which was determined by color change of the muscle after a short time LCx occlusion, was punctured by a 19 G needle with a 16 G sheath. The catheter was passed through the sheath and fixed there after the sheath was removed. In each PmCO₂ measurement experiment, the peak to peak fluctuation in arterial CO₂ tension of the support dog was maintained within 5.2 ± 1.3 mmHg.

For the epicardial ECG recordings, 2 electrodes were sutured to the surface of the left ventricle, near the ultrasonic crystals, in the 2 LAD and LCx perfused areas. An indifferent electrode was positioned at the aortic root. The deviation in ST segment was measured 150 msec after initiation of the QRS complex, as the difference from the T-P segment level. In 1 of 11 cases, epicardial ECG recording was unstable and inadequate for the present analysis. We therefore excluded that case.

In order to ensure that the mean coronary perfusion pressure remained equal to the mean aortic pressure, we made a simple electrical servo system. The signals of both mean pressures were fed into the system and the difference in voltage between them was taken as a feedback signal to regulate the speed of the peristaltic pump. The consequent difference between them could be kept to within ± 2 mmHg when a hemodynamic steady state was reached. This servo system has been described previously.

We recorded LVP, aortic flow, aortic pressure, coronary perfusion pressure, total left coronary and LCx flows and PmCO₂ on a direct pen recorder (San-EI Sokki Rectigraph 8s) and LVP, aortic flow, segment lengths and ECGs on a inkjet recorder (Mingograph Siemens Elema 804). In addition, all of the data were recorded on a data recorder (SONY UFR-71460S).

3) Procedure

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After completion of the experimental preparation, defibrillation was carried out by D.C. counter shock (Mini-defibrillator type 280, Cardiac Recorders, 8-10 joule). Throughout the intervention in each experiment, mean aortic pressure was held constant at a given level (i.e., 90 mmHg in this experiment) by regulating the value of the peripheral resistance in the hydraulic device. Then, using the servo-controlled system, mean coronary perfusion pressure was continuously adjusted to the mean aortic pressure.

After observing 30-60 minutes of hemodynamic steady state at low LVEDP, we began measuring all previously mentioned variables. Thereafter, we elevated this low LVEDP into the middle and then the high LVEDP levels and repeated the measurements (i.e., Pre-ischemic stage). We returned LVEDP to the low level which we called Intermediate Control. After recording all of the parameters again in this Intermediate Control state, gradual LCx stenosis was performed at this low level of LVEDP with the screw type occluder installed in the LCx perfusion line, until the segment length of the LCx area showed an apparent decrease in shortening, but no total systolic bulging and no progressive worsening of the total and regional cardiac function were observed. After attaining a steady state in each variable (about 10 minutes after LCx stenosis), LVEDP was elevated to the middle and then the high levels. However, in 8 of 18 cases, in order to avoid order effects during the Ischemic stage, LVEDP was changed from the low to high, middle and the low again.

We observed a hemodynamic, electrocardiographical and gaseous steady state, for at least 3 to 5 minutes in both the Pre-ischemic and Ischemic stages. To observe such a steady state at each step, 5 to 10 minutes were required especially in the Ischemic stage mainly due to the equilibration of PmCO₂.

4) Data analysis

Instantaneous left ventricular pressure, aortic pressure, aortic flow and segment length were digitized with a digital computer system (Okitac 4300). The analogue data were sampled every 5 msec and averaged for 5 serial beats, during which the variance of peak left ventricular pressure was within 5%. Digitized data were used for the analysis of LVEDP, EDL and shortening of segment length.

The criteria whether to employ an experiment were determined by the stabilities of cardiac out-
TABLE 1. CONTROLLED PARAMETERS AND CORONARY BLOOD FLOW

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-ischemic Stage</th>
<th>LCx Stenosis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mmHg)</td>
<td>Low 9.0 ± 0.7, 6.9 ± 0.7</td>
<td>90.1 ± 0.5, 89.5 ± 0.5</td>
<td>10.8 ± 1.2, 16.3 ± 1.5</td>
</tr>
<tr>
<td>AOP (mmHg)</td>
<td>Low 90.6 ± 0.8</td>
<td>153 ± 15</td>
<td>154 ± 12</td>
</tr>
<tr>
<td>P.P. (mmHg)</td>
<td>Low 68 ± 7</td>
<td>68 ± 7</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>CBF (ml/min)</td>
<td>Low 152 ± 15</td>
<td>153 ± 14</td>
<td>154 ± 12</td>
</tr>
<tr>
<td>TCFB (ml/min)</td>
<td>Low 68 ± 7</td>
<td>68 ± 7</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>LCxF (ml/min)</td>
<td>Low 68 ± 7</td>
<td>68 ± 7</td>
<td>68 ± 7</td>
</tr>
</tbody>
</table>

Note: All values are means ± S.E. (n = 18). * p < 0.01; ** p < 0.001

Mean LCx flows at low, middle and high LVEDPs without LCx stenosis were 67 ± 8, 68 ± 8 and 68 ± 7 ml/min. After LCx stenosis, this flow decreased to 25 ± 3, 25 ± 3 and 26 ± 3 ml/min at each corresponding LVEDP level. The rate of LCx flow reduction, compared to the Pre-ischemic stage, was 60.6 ± 4.5%. On the other hand, LAD flow showed no significant change during any experimental run.

An obvious increase in cardiac output (CO) was observed in step with the elevation of LVEDP in the Pre-ischemic stage (Table II, Fig.2). The mean values of the 18 cases at low, middle and high LVEDPs were 876 ± 116, 1413 ± 118 and 1879 ± 152 ml/min, respectively. The LCx stenosis led to a decrease in CO significantly at all levels of LVEDP. There was a significant increase in CO from the low (421 ± 61 ml/min) to the middle LVEDP level (796 ± 103 ml/min, p < 0.05), but no further significant rise was observed from middle to the high LVEDP level.

RESULTS

1) Systemic and coronary hemodynamics during preload alteration (Tables I and II)

Mean aortic pressure was kept constant at around 90 mmHg throughout the experiment. Proximal mean coronary perfusion pressure closely followed mean aortic pressure. There was no substantial differences between them (Table I). LVEDP was altered in a stepwise fashion and the values were 6.9 ± 0.7, 10.8 ± 1.2 and 16.3 ± 1.5 mmHg in the Pre-ischemic stage. After LCx stenosis LVEDP showed a similar 3 step change; i.e., 7.1 ± 0.7, 10.7 ± 0.9 and 16.3 ± 1.0 mmHg.

There was no significant difference in each corresponding value, between Pre-ischemic and Ischemic stages.

Mean LCx flows at low, middle and high LVEDPs without LCx stenosis were 67 ± 8, 68 ± 8 and 68 ± 7 ml/min. After LCx stenosis, this flow decreased to 25 ± 3, 25 ± 3 and 26 ± 3 ml/min at each corresponding LVEDP level. The rate of LCx flow reduction, compared to the Pre-ischemic stage, was 60.6 ± 4.5%. On the other hand, LAD flow showed no significant change during any experimental run.

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<table>
<thead>
<tr>
<th>TABLE II CARDIAC OUTPUT AND REGIONAL FUNCTIONS</th>
</tr>
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<tbody>
<tr>
<td>Pre-ischemic stage</td>
</tr>
<tr>
<td>LVEDP mmHg</td>
</tr>
<tr>
<td>C.O. ml/min</td>
</tr>
<tr>
<td>LAD Length</td>
</tr>
<tr>
<td>% EDL</td>
</tr>
<tr>
<td>(13.6 ± 0.8 mm)</td>
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<tr>
<td>% SL</td>
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<tr>
<td></td>
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<tr>
<td>LCx Length</td>
</tr>
<tr>
<td>% EDL</td>
</tr>
<tr>
<td>(11.4 ± 0.5 mm)</td>
</tr>
<tr>
<td>% SL</td>
</tr>
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</table>

mean ± S.E. (n = 18), +: p < 0.05, *: p < 0.01, **: p < 0.001
C.O. = cardiac output; LAD, LCx = the areas perfused by the left anterior descending artery and left circumflex artery, respectively; % EDL = end-diastolic length presented as the percent change of that at low LVEDP in the Pre-ischemic stage, (LAD: 13.6 ± 0.8 mm, LCx: 11.4 ± 0.5 mm); % SL = percent segment length change. See legend of Table I for abbreviations and for significant difference between Pre-ischemic and Ischemic stages.
Fig. 2 The relationship between cardiac output and LVEDP with and without LCx stenosis under constant heart rate and mean aortic pressure. Cardiac output decreased after the LCx stenosis and no significant increase was observed at the higher LVEDPs. LVEDP = left ventricular end-diastolic pressure; open circles: Pre-ischemic stage; closed circles: Ischemic stage.

\[(931 \pm 153 \text{ ml/min})\].

2) Regional function and regional myocardial ischemia during preload alteration (Table II and III)

An example of segment length change is presented in Fig. 3, where the Pre-ischemic stage is shown in the upper panel and LCx stenosis in the lower. The EDL of the LAD and LCx areas increased in accordance with elevated LVEDP during both experimental stages. This increase in EDL caused a rise in SL in all cases except in the LCx area during the Ischemic stage. Table II shows the mean values of percent EDL and percent SL changes in both the LAD and LCx areas. After LCx stenosis there was no substantial increase in %SL (3.9 \pm 2.9, 5.8 \pm 2.2 and 6.5 \pm 1.8\%, respectively) in the LCx area, in spite of lengthened %EDL (103.3 \pm 0.7, 108.6 \pm 1.2 and 111.9 \pm 1.5\%).

Figure 4 demonstrates the considerable change in PmCO\(_2\) and epicardial ECGs when LVEDP was changed from 6 to 9 mmHg with LCx stenosis. LCx stenosis (indicated by an arrow) caused an increase in PmCO\(_2\) (from 42 to 64 mmHg) downward deflection in the figure.

**Table III** MYOCARDIAL PCO\(_2\), AND ST LEVEL

<table>
<thead>
<tr>
<th>Pre-ischemic stage</th>
<th>LCx stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>LVEDP mmHg</td>
<td>PmCO(_2) mmHg</td>
</tr>
<tr>
<td>2.1 \pm 1.4</td>
<td>44.0 \pm 1.4</td>
</tr>
<tr>
<td>0.49 \pm 0.72</td>
<td>0.003 \pm 0.41</td>
</tr>
<tr>
<td>0.29 \pm 0.33</td>
<td>0.64 \pm 0.5</td>
</tr>
</tbody>
</table>

**Legend** for abbreviations and for the statistical significance between the Pre-ischemic and Ischemic stages.

*mean \(\pm\) S.E. (n = 11) \(\pm\) p < 0.05, **p < 0.01, ***p < 0.001*

\[PmCO_2 = \text{micromolar carbon dioxide tension in LCx area.} \]

\[ST = \text{the deviation of ST segment recorded at the epicardial surface of both areas.} \]
Moreover, the elevation of LVEDP (from 6 to 9 mmHg) induced a marked rise in PmCO\(_2\) from 64 to 84 mmHg, and a slight rise appeared on further elevation of LVEDP (from 9 to 15 mmHg). The mean values of PmCO\(_2\) (n = 11) were plotted on the ordinate, as a function of LVEDP (Fig. 5). In the Pre-ischemic stage (open circles), PmCO\(_2\) did not increase significantly following preload increase, although there was a little increase from the middle to the high LVEDP stage (43.7 ± 1.7 to 50.0 ± 2.9 mmHg). After LCx stenosis (solid circles), the corresponding values of PmCO\(_2\) were higher than those of the Pre-ischemic stage. There was also a significant increase in PmCO\(_2\) from low (52.3 ± 3.3 mmHg) to high (66.5 ± 4.1 mmHg, p < 0.01), and middle (57.5 ± 4.1 mmHg) to high LVEDP (p < 0.05).

The ST changes are presented in the lower panels in Fig. 4, numbered from (1) to (4). The ST segment of LCx-ECG rose markedly after the LCx stenosis (from (1) to (2)) and the deviation was dependent on the level of LVEDP, i.e., the higher the LVEDP, the higher the ST level (from (2) to (4)). The mean ST deviations (n = 10) in epicardial ECG in both the LAD and LCx perfused areas are plotted in Fig. 6, as a function of LVEDP. In the Pre-ischemic stage (LCx area: open triangles, LAD area: open squares), ST levels of both areas were almost constant, near the base line. LCx stenosis induced marked ST elevation of the LCx area (solid triangles, 3.52 ± 0.72 mV, p < 0.05) and a slight depression of the LAD area solid squares. This ST elevation was re-
markably influenced by the LVEDP levels as well as PmCO₂. Namely, the mean ST values in the LCx area at low, middle and high LVEDPs were $3.52 \pm 0.72$, $4.40 \pm 1.22$ and $7.69 \pm 2.0$ mV, respectively. The ST level in the LAD area, however, was not significantly influenced, as shown in Fig. 6 and Table III.

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Fig. 5 The relationship between myocardial carbon dioxide tension (PmCO₂) and LVEDP with and without LCx stenosis. After LCx stenosis (closed circles), PmCO₂ increased significantly, and when LVEDP was elevated, it further increased. However, there was no significant change in PmCO₂ in the Pre-ischemic stage (open circles). See also Table III.

DISCUSSION

Although many studies concerning the effects of preload alteration on cardiac performance are available, there has been little work in which the influences of preload alone on regional and global functions of ischemic myocardium were simultaneously investigated. In the present study, we clearly showed that the level of preload itself influences ischemic injury; with mild LVEDP elevation, global cardiac function improved without severe aggravation of ischemic injury, while at a much higher elevation of LVEDP, global and regional functions did not improve any further and the degree of ischemia was significantly worsened.

Regional myocardial ischemia and mechanical function in preload alteration

As shown in Table II, SLs of both the LAD and LCx areas in the Pre-ischemic stage increased with an increase in EDL, although SL in the LAD area showed a non-significant increase from middle to high LVEDP. Also, cardiac output without LCx stenosis increased, depending on the increase in LVEDP.

After LCx stenosis, the contractile state of this LCx area definitely decreased. There was no significant augmentation of mechanical performance in the LCx area by preload elevation. Both increased PmCO₂ and ST level in the LCx area, following LCx stenosis, were further elevated, accompanied with an increase of LVEDP. Thus, failure to observe a significant increase in SL at middle or high LVEDP indicated an additional depressing effect. Since these data were obtained under constant heart rate and mean aortic pressure, we assumed that ischemic injury after LCx stenosis was aggravated mainly by the preload increase, although the effects of changes in true afterload were not determined. One possible reason why myocardial ischemic injury worsened following a large elevation of LVEDP may be as follows; since the study involved a fixed and rigid stenosis with nearly constant flow, considerably more ischemia may have developed because the oxygen demand of

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the myocardium was increasing with filling of the ventricle. Moreover, it may be partly attributable to an increase in afterload through lengthened EDL, although not significantly different from that at corresponding pre-ischemic LVEDPs. Cardiac output also did not increase significantly at higher LVEDPs after LCx stenosis, partly because of the worsening of ischemic injury in LCx area and partly because of the lack of compensatory hyperfunction in the non-ischemic area in the isolated heart (Table II).

Methodological considerations

We used isolated perfused canine hearts which enabled us to investigate preload change independently of other hemodynamic reactions brought about successively, because: (1) mean aortic pressure (= mean coronary perfusion pressure) and heart rate were kept constant during the intervention. (2) Since the right ventricular free wall and also the pericardium were removed, there was no mechanical interaction between the two ventricles. (3) Reflex and/or neurohumoral changes are not involved during the intervention. However, in our experiment there are some points to be discussed.

First, although mean aortic pressure (= coronary perfusion pressure) was regulated to 90 mmHg, instantaneous pressure was not controlled. Accordingly, systolic wall stress or actual afterload may not have been constant throughout the intervention. Particularly, for regional systolic wall stress in the ischemic LCx area, the stress may be affected by not only instantaneous systolic pressure change but also geometrical and segmental length change due to altered diastolic properties. The present results, obtained only at constant mean aortic pressure, may not be fully consistent with those obtained at constant systolic wall stress, although the results of them are not likely to be different from each other in principle.

Second, we must consider the stability of an excised perfused heart preparation. The stability of the preparation during ischemia has also been discussed in our previous experiments using a similar degree of LCx stenosis. As shown in Tables I, II and III, no significant difference in the various variables was found, at low LVEDP level, between the Pre-ischemic and Intermediate Control stage. The time spent for the whole intervention study was within one hour, and within this time interval the values of mechanical and metabolic parameters at the same low LVEDP did not differ and, as described in "METHODS", returned to almost the same level 10 minutes after releasing the LCx stenosis. Thus, the time course effect, if any, seemed to be minimal.

Third, for evaluating the severity of ischemic injury, ECG-ST level and PmCO₂ were employed. However, ST elevation may not necessarily indicate aggravation of ischemic injury, as pointed out by Holland. According to his theory, ST level is determined by ischemic severity and by a solid angle. Solid angle is determined by the ischemic area and the position of an electrode. We could not confirm that the ischemic area was not changed by the preload elevation. It has been also reported that the myocardial flow distribution is clearly modified by preload alteration. However, the large elevation of ST level may be mainly brought by the change in ischemic severity. The results of the PmCO₂ supported the worsening of the ischemic severity in preload elevation. The mean values of PmCO₂ were almost comparable with those of the other reports.

Fourth, there is a possibility that mitral regurgitation occurs at an elevated LVEDP level in an isolated heart. Therefore, we examined left atrial B-mode echogram in several cases in which the sufficiently shaken indocyanin green solution was injected into the left ventricle via the pressure catheter at three levels of LVEDP. The examination revealed that the significant regurgitation did not occur even at the highest LVEDP level.

Finally, we have demonstrated the possibility that reasonable reduction of a highly elevated preload leads to alleviation of ischemic injury without introducing significant depression of mechanical performance. It should be noted however that these results were obtained under anesthetized, strictly controlled experimental conditions. Therefore, the absolute values obtained in the present study, (i.e., cardiac output, LVEDP, aortic pressure and so on) are not directly available to clinical settings in which many parameters are linked together. Thus, if aortic pressure (i.e., driving pressure) greatly decreases following preload reduction, serious problems such as perfusion mediated disturbance, especially on the ischemic myocardium may arise, while reducing the oxygen demand of the heart. Thus, further investigation will be needed to determine how much preload reduction should be done in individual cases. In this sense, our study indicated the principles relating the effects

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of preload alteration on the ischemic myocardium and those on global and regional cardiac function, in ischemia.

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