Effects of Afterload Reduction on Global Left Ventricular and Regional Myocardial Functions in the Isolated Canine Heart with Stenosis of a Coronary Arterial Branch

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SUMMARY We examined the effects of graded reduction of afterload on the global left ventricular and regional myocardial functions as well as coronary hemodynamics in hearts with regional ischemia. We used isolated, paced canine hearts that were loaded with a hydraulic system that simulated the aortic input impedance of the dog's arterial tree. The loading conditions could be quantitatively and sequentially changed by the reduction of the systemic vascular resistance of the hydraulic system, while the preload was kept constant using a variable-height reservoir connected to the left atrium. The heart was perfused with arterial blood from a support dog. Mean coronary perfusion pressure was maintained equal to mean aortic pressure (AoP) by a servo-controlled pump. Then, the left circumflex branch was constricted to an approximate 50% flow reduction of the preischemic control condition. The myocardial lengths at ischemic and nonischemic regions were measured with two pairs of ultrasonic crystals.

In the hearts without ischemia, cardiac output continued to increase, from 535 ± 14 to 1181 ± 74 ml/min (p < 0.01), as mean AoP decreased from 111 ± 4 to 52 ± 3 mm Hg (p < 0.01), although mean coronary blood flow decreased by approximately 50%. During regional ischemia, at control pressures, performance of the ischemic region diminished from 0.94 ± 0.15 to 0.77 ± 0.15 mm (p < 0.05). With a small decrease in afterload, from 98 ± 6 to 86 ± 3 mm Hg, performance improved slightly as in the normal region. With a larger reduction in afterload, from 86 ± 3 to 55 ± 6 mm Hg, performance of the ischemic region decreased from 0.77 ± 0.15 to 0.61 ± 0.15 mm (p < 0.05) while cardiac output increased. Thus, there appears to be a bimodal change in performance: a baseline performance, perfusion pressure-mediated decrease and a second, afterload-modulated change.

THE REDUCTION of aortic blood pressure (AoP) in the heart with myocardial ischemia lowers left ventricular tension and myocardial metabolic requirements, and decreases coronary blood flow at the same time. Thus, the reduction of AoP has both favorable and unfavorable myocardial effects. Therefore, whether or not the AoP should be decreased is important for the treatment of patients with coronary arterial stenosis.

Many investigators have reported the relationship between regional coronary blood flow and the mechanical function in an experimental model in which the afterload pressure was not controlled. Additionally, the effect of the alteration in AoP on ischemic myocardial function has been reported in the heart with an occlusion of a coronary arterial branch. However, there have been only a few reports concerning the relationship between afterload pressure and ischemic myocardial function in a heart with an incomplete coronary stenosis rather than a complete occlusion.

Sasayama et al. reported that the reduction of AoP aggravated the ischemic myocardial function and its elevation improved it in a heart with a stenosis of the coronary arterial branch. However, Wyatt et al. reported that elevation of AoP did not significantly im-

prove ischemic myocardial function in a heart with a same degree of stenosis and with a comparable ischemic area. In contrast, Lekven and Kiil also reported that the elevation of systolic ventricular pressure decreased the shortening of the ischemic myocardium, although the ischemic lesion was more extensive than that in the reports by Sasayama et al. and Wyatt et al. Thus, how the alteration in AoP affects the ischemic myocardial function is not clear.

Using isolated heart preparations, we studied how the alteration in AoP affects regional ischemic myocardial function and global ventricular function, and how the magnitude of its effect is altered by the level of aortic pressure in the presence of a flow-limiting stenosis of a coronary arterial branch.

Methods

Surgical Preparation (fig. 1)

Nine mongrel dogs that weighed 14.5-19.0 kg (average 16.1 kg) were anesthetized with sodium pentobarbital, 25-30 mg/kg. Respiration was controlled by a Harvard ventilator through an endotracheal tube; a thoracotomy was performed bilaterally at the third intercostal space. A Gregg-type cannula was inserted through the right carotid artery to the ascending aorta and was tied with a silk thread at the brachiocephalic artery. The left common carotid and subclavian arteries were ligated, as was the descending aorta. Just after starting coronary perfusion of the heart with blood from the femoral artery of a support dog that was also anesthetized with sodium pentobarbital, using a peri-

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The experimental setup. The isolated heart is loaded with a hydraulic system of the input impedance of the systemic arterial tree of the dog. L = the inertial component (representing the inertia of the blood); Rc = the resistance component (representing the characteristic impedance); C = the capacitance component (representing the total arterial compliance); Rp = the resistance component (representing the total peripheral resistance). A variable-height large reservoir is connected to the left atrium through the pulmonary vein. The heart is perfused with the arterial blood from the support dog, using a servo-controlled peristaltic pump. The coronary venous blood is returned to the support dog.

The aorta was cut at about 1.5 cm from the aortic valve and an adaptor of the hydraulic loading system was connected to the aorta. This system simulated the input impedance of the dog's systemic arterial tree. The characteristics of the system have been described. Briefly, this system consists of four components: the inertial component (L), total arterial compliance (C), characteristic resistance component (Rc), and total peripheral resistance component (Rp). In this study, we kept the values of L, C and Rc constant at their respective physiologic ranges (L = 10 dyn-sec^2/cm^3, C = 2 × 10^{-4} dyn^-1-cm^3 and Rc = 0.2 × 10^3 dyn-sec-cm^-5), as was done in our previous study. Initially, we set the Rp at 10.5 × 10^4 dyn-sec-cm^-5 (control Rp) and then changed its value from 16.1 × 10^3 to 3.3 × 10^3 dyn-sec-cm^-5 in a stepwise fashion.

A wide cannula was inserted through the pulmonary vein and was connected to a variable-height large reservoir, where the saline temperature was kept constant at 37 ± 0.5°C. The heart was defibrillated by direct current. The saline ejected by the left ventricle into the hydraulic loading system was pumped back into the reservoir (fig. 1).

Heart rate was kept constant at 100–130 beats/min by bipolar electrical stimulation (Nihon Kohden, model SEN-7103M). Furthermore, two epicardial electrodes were sutured at the surface of the left ventricle for ECG recordings: one near the center of the distribution of the left anterior descending branch (LAD) and the other near the center of the distribution of the LCx branch.

During these procedures, the perfusion pressure (PP) was continuously measured from the side arm of the perfusion line and maintained between 70 and 100 mm Hg. Coagulation was prevented with heparin (10,000 U initial injection and 5000 U every hour thereafter).

Two support dogs were used for each experiment: one to support the heart during the surgical preparation period or the priming of the hydraulic loading system and the other to support the heart during the experiment.

Arterial blood of the support dog was obtained from the side arm of the perfusion line at frequent intervals, and the pH, Po2, Pco2, and hemoglobin were measured (Radiometer, BMS-MK 2, PHM72-MK2 Digital Acid-Base Analyzer and Erma hemoglobin meter type 303A). We corrected the arterial blood gas or hemoglobin by infusion of sodium bicarbonate, ventilatory adjustment with O2 inhalation, and blood transfusion. Thus, we maintained the arterial Po2 above 75 mm Hg, the pH at 7.32–7.45, and the hemoglobin at 10–15 g/dl throughout the experiment. The temperature of the arterial blood for coronary perfusion was also maintained at 37.0 ± 0.5°C by a thermostatic system. Arterial and central venous pressures were continuously monitored and maintained within their normal ranges. During surgical preparation, additional sodium pentobarbital was given to the support dog after the initial injection, if necessary; however, it was not given during measurements in order to maintain the effect of the anesthetic agent on the cardiac performance constant.

Measurements and Calculations (fig. 2)

Left ventricular pressure (LVP) was measured with a stiff polyethylene cannula inserted into the left ventricular cavity at the apex, and AoP was also measured at the inlet of the hydraulic loading system, using strain-gauge pressure transducers (Toyo Sokki, MPU 0.5). In addition, left coronary PP was measured from the side arm of the perfusion line. The zero-pressure reference was taken at the middle level of the heart.

Aortic flow (AoF) was measured at the inlet of the hydraulic loading system, using a magnetic flowmeter (Nihon Kohden, model MF46). Mean left coronary blood flow (Cor. F_total) was measured with an extracorporeal-type probe (3 mm in diameter, Nihon Kohden, type FF-030T) positioned in the perfusion line. Fur-
thermore, a corporeal-type probe (2 mm in diameter, Nihon Kohden, type FS-020T) was positioned around the LCx branch at its origin and mean LCx blood flow (Cor. \( F_{\text{LCx}} \)) was recorded using an electromagnetic flowmeter (fig. 2). The AoF was presumed at be 0 during diastole and the coronary flow base line was established by momentary occlusion. The values of mean LAD blood flow (Cor. \( F_{\text{LAD}} \)) were calculated by subtracting the mean Cor. \( F_{\text{LCx}} \) value from the mean Cor. \( F_{\text{Total}} \). The frequency response of the systems of the pressures and flows measurements has been described.\(^{17}\) Cardiac output (CO) was measured by collecting an amount of the ejected saline over 20 seconds.

To measure regional dimensions, two pairs of miniature (1.5–2.0 mm in diameter) ultrasonic crystals were implanted subendocardially, as proved by post-mortem examination. The crystals of each pair were separated by 1–2 cm in two locations: one, the LCx segment in the center of the distribution of the LCx branch; the other, the LAD segment in the center of the distribution of the LAD branch. We built the basic ultrasonic dimensioning circuitry according to the design of Theroux et al.\(^{18}\) The 5-MHz crystals were fabricated from lead titanate-zirconate piezo ceramic and were soldered to stainless-steel wires. The crystals were manipulated to achieve a position in the myocardium where an acceptable ultrasonic signal was obtained as visualized on an oscilloscope. End-diastolic dimensions were defined at the beginning of the uptake of the LVP, and end-systolic dimensions at the end of the ejection which was determined from the AoF curve. Systolic shortening was calculated as the difference between these two lengths. Each measured value was normalized to a 10-mm segment length by dividing the observed length by the control end-diastolic segment length and multiplying by 10. This method of normalization of segment dimension was chosen because the distance between each pair of crystals was variable and arbitrary in relation to the actual circumference of each heart, thus making it more convenient to compare segmental responses among different hearts.

We recorded the tracings of pressures, flows, regional dimensions and ECG on a direct-writing pen recorder (Sanei Sokki, six-channel Rectigraph and eight-channel Rectigraph) and a magnetic analog tape recorder (Sony Magnescale Inc., model UFR 71460S).

All values of variables measured were expressed as mean ± SEM. Statistical analysis of the data was performed using an analysis of variance and multiple-comparison test.

Servo-controlled Perfusing System

We made a simple servo-controlled coronary perfusing system to simulate the physiologic perfusion condition. We attempted to make the mean PP equal to the mean AoP after any change in the mean AoP. The electrical signals of the PP and the AoP were fed into the system and the difference in voltage between the mean values of these signals (mean PP minus mean AoP) was taken as a feedback signal for the peristaltic pump. The high voltage of the feedback signal decelerates the peristaltic pump, and the pump speed is not altered when the feedback signal is at 0 voltage. As a result, the time constant of the mean PP was 10–15 seconds when the Rp value or the peak LVP was changed in a stepwise fashion (fig. 3). The difference between the AoP and the mean PP was maintained within 2 mm Hg when the hemodynamic steady state was reached.

Experimental Protocol

In eight of the nine hearts without a stenosis of the coronary artery, we first obtained the data for the hemodynamics and regional function. Under this condition, we changed the Rp from \( 16.1 \times 10^3 \) to \( 3.3 \times 10^3 \) dyn-sec-cm\(^{-5} \) with a constant left ventricular end-diastolic pressure (LVEDP) and heart rate. The Rp was changed in a stepwise fashion at intervals of 2–3 minutes (fig. 3).

Second, we obtained the data after producing a stenosis of the LCx branch. In eight of the nine hearts, a screw-driven metal clamp was placed around the LCx branch just distal to the flow probe so that the mean Cor. \( F_{\text{LCx}} \) was reduced to 50% of the control value, which was obtained at \( 10.5 \times 10^3 \) dyn-sec-cm\(^{-5} \) of Rp. Particular care was taken that no coronary branches were present between the clamp and the flow probe. About 5 minutes after constriction of the LCx branch, we observed that a hemodynamic steady-state had been reached. Thereafter, we changed the Rp sequentially from \( 16.1 \times 10^3 \) to \( 3.3 \times 10^3 \) dyn-sec-cm\(^{-5} \).
LAD and LCx regions was also measured and were 104 ± 4% and 95 ± 4%, respectively. At the end of the second experimental protocol, we removed the clamp from the LCx branch and remeasured CO and systolic shortening of the two regions for control Rp and LVEDP. They were 88 ± 4%, 104 ± 6% (LAD region) and 90 ± 9% (LCx region) of their respective values at the beginning of the experiment.

At the conclusion of each experiment, we occluded the LCx branch and injected indocyanine green from the Gregg-type cannula. Thus, we determined the ventricular muscle weights perfused by the LAD and LCx branches (58 ± 5 and 43 ± 3 g, respectively). Pressure drop by the Gregg-type cannula was 4 mm Hg at a flow rate of 100 ml/min.

**Results**

Figure 3 shows the representative tracings of the systemic and coronary hemodynamics. The Rp was reduced from 10.5 × 10³ to 1.9 × 10³ dyn-sec-cm⁻⁵ when there was a stenosis of the LCx branch. The mean Cor. F_{LCx} was reduced from 85 to 40 ml/min by the screw-driven metal clamp at an Rp of 10.5 × 10³ dyn-sec-cm⁻⁵. Thereafter, peak LVP and mean AoP gradually decreased and mean AoF increased. At the same time, the mean PP decreased because of the servo-controlled pump, after a change in mean AoP. As a result, the mean Cor. F_{Total} decreased in accordance with a decrease in mean AoP. A hemodynamic steady state was observed 2 minutes after producing a stenosis in the LCx branch. After the hemodynamics reached a steady state, Rp was reduced from 10.5 × 10³ to 6.2 × 10³ dyn-sec-cm⁻⁵ in a stepwise fashion. Peak LVP decreased in a stepwise fashion, and mean PP was automatically set equal to mean AoP 20 seconds after the stepwise change of Rp. Mean AoF increased from 640 to 885 ml/min and mean Cor. F_{Total} and mean Cor. F_{LCx} simultaneously decreased. Thus, the Rp was changed in a stepwise fashion up to 1.9 × 10³ dyn-sec-cm⁻⁵. At Rp values of 10.5 × 10³ to 3.3 × 10³, but not at 1.9 × 10³ dyn-sec-cm⁻⁵, a hemodynamic steady state was observed.

Figure 4 shows the simultaneous tracings of the pressures, flows, segmental lengths and ECG. The systolic shortening of the LCx region at an Rp of 10.5 × 10³ dyn-sec-cm⁻⁵ decreased after stenosis of the LCx branch compared with that in the preischemic period at the same Rp. When the Rp was elevated from 10.5 × 10³ to 16.1 × 10³ dyn-sec-cm⁻⁵, the systolic shortening in the LCx region decreased in accordance with an increase in the peak LVP. Furthermore, it decreased with the reduction of Rp from 10.5 × 10³ to 6.2 × 10³ dyn-sec-cm⁻⁵. At 4.7 × 10³ and 3.3 × 10³ dyn-sec-cm⁻⁵ of Rp, bulging in the early systolic phase was observed, and systolic shortening in the LCx region decreased.

In contrast, systolic shortening in the LAD region continued to increase with the reduction of Rp from 16.1 × 10³ to 3.3 × 10³ dyn-sec-cm⁻⁵. Peak LVP progressively decreased and peak AoF increased with the reduction of Rp from 16.1 × 10³ to 3.3 × 10³ dyn-sec-cm⁻⁵.
MYOCARDIAL FUNCTION IN AFTERLOAD REDUCTION/Isoyama et al.

Figure 4. Simultaneous tracings of pressures, flows and segmental lengths. LVP = left ventricular pressure; AoP = aortic pressure; AoF = aortic flow; SLAD = segment length in the center of the distribution of the left anterior descending branch; SLCFX = segment length in the center of the distribution of the left circumflex branch; ECGCFX = epicardial ECG over the distribution of the left circumflex branch.

In addition, the ST segment of the ECG at the LCx region was depressed after LCx stenosis; its depression became greater as Rp decreased.

Figure 5 and table 1 show the systemic and coronary hemodynamics for eight hearts both with and without LCx stenosis. Although the mean Cor FLCX and mean Cor LAD in the hearts without LCx stenosis decreased by approximately 50% with the reduction of Rp from 16.1 × 10³ to 3.3 × 10³ dyne-sec-cm⁻³ (from 71 ± 6 to 38 ± 8 ml/min, and from 57 ± 6 to 29 ± 7 ml/min, respectively), the CO continued to increase, from 535 ± 14 to 1181 ± 74 ml/min. Simultaneously, the peak LVP and the mean AoP decreased from 137 ± 5 to 80 ± 5 mm Hg and from 111 ± 4 to 52 ± 3 mm Hg, respectively. After stenosis of the LCx branch, the mean Cor FLCX was reduced to approximately 50% of its preischemic value at 10.5 × 10³ dyne-sec-cm⁻³ of Rp (from 58 ± 6 to 28 ± 3 ml/min), and the CO decreased from 758 ± 10 to 627 ± 20 ml/min (p < 0.01). The peak LVP and the mean AoP also decreased, from 126 ± 3 to 109 ± 4 mm Hg (p < 0.01) and from 101 ± 2 to 86 ± 3 mm Hg (p < 0.01), respectively. In the hearts with the LCx stenosis, the peak LVP and the mean AoP progressively decreased with the reduction of Rp; the CO continued to increase from 482 ± 26 to 1050 ± 71 ml/min, as it did in the hearts without LCx stenosis. The mean Cor FLCX in the hearts with LCx stenosis seemed to be greater than in the hearts without LCx stenosis despite a decrease in the mean AoP. However, this change was not statistically significant.

Figure 6A shows the relationship between the mean AoP and the CO. In the hearts without LCx stenosis, the CO continued to increase with the reduction of the mean AoP in a roughly linear fashion. The CO in the hearts with LCx stenosis also increased with the reduction of mean AoP, and this linear relationship shifted to the left and downward.

The systolic shortening in both the LAD and LCx regions continued to increase with the reduction of Rp or mean AoP in the hearts without ischemia (table 2, fig. 6B). Except in the LCx region, these changes were statistically significant (p < 0.05 at an Rp of 4.7 × 10³; p < 0.01 at an Rp of 3.3 × 10³ dyne-sec-cm⁻³). After stenosis of the LCx branch at an Rp of 10.5 × 10³ dyne-sec-cm⁻³, systolic shortening of the LCx region decreased to 76 ± 6% of the preischemic control value, from 0.94 ± 0.15 to 0.77 ± 0.15 mm. Systolic
TABLE 1.  
Global Ventricular Function for Eight Hearts Both With and Without a Coronary Stenosis

<table>
<thead>
<tr>
<th>Rp (× 10^3 dyn-sec-cm^-5)</th>
<th>16.1</th>
<th>10.5</th>
<th>6.2</th>
<th>4.7</th>
<th>3.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stenosis</td>
<td>535 ± 14</td>
<td>758 ± 10</td>
<td>968 ± 37</td>
<td>1050 ± 53</td>
<td>1181 ± 74</td>
</tr>
<tr>
<td>With stenosis</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak LVP (mm Hg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stenosis</td>
<td>137 ± 5</td>
<td>126 ± 3</td>
<td>107 ± 3</td>
<td>93 ± 5</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>With stenosis</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AoP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stenosis</td>
<td>111 ± 4</td>
<td>101 ± 2</td>
<td>78 ± 3</td>
<td>64 ± 4</td>
<td>52 ± 3</td>
</tr>
<tr>
<td>With stenosis</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cor.F_LAD (ml/min)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stenosis</td>
<td>71 ± 6</td>
<td>77 ± 11</td>
<td>58 ± 8</td>
<td>49 ± 10</td>
<td>38 ± 8</td>
</tr>
<tr>
<td>With stenosis</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cor.F_LCx (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stenosis</td>
<td>57 ± 6</td>
<td>58 ± 6</td>
<td>50 ± 12</td>
<td>37 ± 9</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>With stenosis</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

p = statistical significance between the mean values in the hearts without and those with stenosis at the same Rp; p' = statistical significance between the mean values at a given Rp and at an Rp of 10.5 × 10^3 dyn-sec-cm^-5 in the hearts with and without stenosis.

Abbreviations: Rp = peripheral resistance; CO = cardiac output; LVP = left ventricular pressure; AoP = mean aortic pressure; Cor.F_LAD and Cor.F_LCx = mean coronary blood flow of the left anterior descending and left circumflex branches, respectively.

shortening of the LCx region during regional ischemia decreased from 76 ± 6% to 65 ± 9% with the elevation of mean AoP from 86 ± 3 (at an Rp of 10.5 × 10^3) to 98 ± 6 mm Hg (at an Rp of 16.1 × 10^3 dyn-sec-cm^-5); however, this change was not statistically significant. It decreased again, from 76 ± 6% to 56 ± 10%, with the reduction of mean AoP from 86 ± 3 (at an Rp of 10.5 × 10^3), to 55 ± 6 mm Hg (at an Rp of 4.7 × 10^3 dyn-sec-cm^-5) (p < 0.05). The decrease in the systolic shortening of the LCx region was statistically significant below this level of mean AoP or Rp. However, the systolic shortening of the LAD region in the hearts with LCx stenosis increased with the reduction of mean AoP in a roughly linear fashion, as it did in the hearts without LCx stenosis. At the same Rp, the systolic shortening of the LAD region in the hearts with LCx stenosis was relatively greater than it was in the hearts without LCx stenosis. In addition, at lower

FIGURE 6. (A) the relationship between mean aortic pressure (AoP) and cardiac output (CO). (B) the relationship between AoP and the systolic shortening. Systolic shortening is expressed as a percentage of the control condition (Rp = 10.5 × 10^3 dyn-sec-cm^-5 and without coronary stenosis). Solid lines and dotted lines indicate the location of the left anterior descending and left circumflex (LAD and CFX) regions. Values are mean ± SEM.
Table 2. Regional Myocardial Function of the Two Regions

<table>
<thead>
<tr>
<th>Rp (× 10^3 dyn-sec-cm^-2)</th>
<th>LAD region</th>
<th>16.1</th>
<th>10.5</th>
<th>6.2</th>
<th>4.7</th>
<th>3.3</th>
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<tbody>
<tr>
<td>SS (mm) Without stenosis</td>
<td>1.00±0.13</td>
<td>1.10±0.13</td>
<td>1.13±0.18</td>
<td>1.31±0.17</td>
<td>1.33±0.14</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>EDL (mm) Without stenosis</td>
<td>10.06±0.09</td>
<td>10.00</td>
<td>9.83±0.07</td>
<td>9.86±0.09</td>
<td>9.86±0.09</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
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<tr>
<td>LCx region SS (mm) Without stenosis</td>
<td>0.80±0.18</td>
<td>0.94±0.15</td>
<td>1.05±0.14</td>
<td>1.07±0.16</td>
<td>1.07±0.20</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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<tr>
<td>p'</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>EDL (mm) Without stenosis</td>
<td>10.10±0.08</td>
<td>10.00</td>
<td>9.88±0.12</td>
<td>9.91±0.07</td>
<td>9.87±0.06</td>
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<tr>
<td>p'</td>
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<td>NS</td>
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<td>p'</td>
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Values are mean ± SEM.
See table 1 for explanation of p values.
Abbreviations: Rp = peripheral resistance; SS = extent of systolic shortening; EDL = end-diastolic length; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery.

levels of mean AoP, systolic shortening in the hearts with LCx stenosis was greater than it was in the hearts without LCx stenosis for the same mean AoP. However, this change was not statistically significant. End-diastolic length of the two regions did not change significantly during LCx stenosis and afterload reduction (table 2).

Discussion

Few reports are available concerning the relationship between the afterload and the ischemic myocardial function in the presence of a flow-limiting stenosis, rather than occlusion, of a coronary arterial branch. Furthermore, these reports have many limitations. In the reports by Sasayama et al.13 and Lekven et al.,12 preload was not controlled; in fact, the LVEDP or end-diastolic segment length increased as afterload pressure increased. Therefore, we must consider the important effect of the preload on the regional function of the ischemic myocardium.14 Sasayama et al.13 changed the afterload by using sodium nitroprusside; therefore, we must consider its effect not only on afterload, but also on coronary hemodynamics.19

We recently reported that cardiac output increased with afterload reduction, but decreased with further reduction under the restricted perfusing condition that simulated the pathologic perfusion of the left main coronary artery.17 However, we did not examine the effect of afterload reduction on regional function of the ischemic myocardium in the hearts with a stenosis of a coronary arterial branch. Because shortening of both nonischemic and ischemic myocardium contributes to the development of afterload, regional function of the ischemic myocardium may be modified by the function of the nonischemic myocardium, and the effect of afterload reduction on the ischemic myocardium in a globally ischemic heart may differ from that in a regionally ischemic heart. Therefore, we designed this study to examine the effect of the reduction of systemic vascular resistance on global and regional myocardial function during regional ischemia.

Limitations of the Experimental Model

The cardiac output and regional function at the end of the first experimental protocol for the same control condition returned to their respective initial values. Furthermore, they were only slightly depressed after the second protocol. Therefore, the total and regional function of the isolated heart in our experimental model was satisfactorily stable and reversible during the measurement.

Systolic shortening of the LCx region before regional ischemia was slightly less than that of the LAD region. However, we eliminated these effects by comparing systolic shortening of the LCx region before ischemia and during ischemia in relation to afterload pressure (fig. 6B).

Regardless of the heart size and body weight of the dog, we determined the LVEDP for each heart at a value that produced a mean AoP of 100 mm Hg at an Rp of 10.5 × 10^3 dyn-sec-cm^-2, or that produced the same CO for each heart at the same Rp. Therefore, the LVEDP for each heart varied from 3 to 12 mm Hg.

We could observe reactive hyperemia after we stopped the coronary perfusion for either a 15- or 30-second period. In addition, after a stenosis of the LCx branch, the mean coronary blood flow of the LAD branch at the same Rp increased despite the reduction of mean AoP or PP (fig. 4, table 1). The extent of autoregulation of the coronary blood flow to the reduc-
tion of PP was small and the total coronary flow was high at control, compared with those usually observed in an open-chest dog. 17

Although our experimental model has limitations, we can analyze how preload, afterload and coronary perfusion pressure affect cardiac performance. We could study the regional function of the ischemic myocardium at a wider range of Rp values than physiologic values, since we could relieve the heart from ischemia at appropriate intervals.

The Relationship between Rp or Mean AoP and Regional Myocardial Function

Afterload pressure and mean coronary blood flow determine the degree of shortening of both ischemic and nonischemic myocardium. In addition, the extent of regional myocardial shortening may vary by location. Therefore, we determined the effect of afterload pressure on ischemic myocardial function by comparing the shortening between the hearts before and after stenosis in the same region (table 2) and at the same afterload pressure (fig. 6B).

In our study, at control pressures, performance of the ischemic region diminished, yet with a small decrease in afterload, performance improved as in the nonischemic region. With a larger reduction in load, performance decreased. Thus, there appears to be a bimodal change in performance: a baseline performance, perfusion pressure-mediated decrease and a second, afterload-modulated change.

In the report by Sasayama et al., 13 systolic shortening of the ischemic myocardium produced by a stenosis that resulted in an approximately 50% reduction in flow decreased with the reduction of left ventricular systolic pressure in the range of 89 to 128 mm Hg. However, Wyatt et al. 14 reported that systolic shortening of the ischemic myocardium did not increase with the elevation of mean AoP from 95 to 127 mm Hg in hearts that had a comparable degree of stenosis and a similar ischemic area. In contrast, Lekven and Kiil 15 reported that systolic shortening of the ischemic myocardium increased with reduction of left ventricular systolic pressure in the range of 93 to 135 mm Hg, although the ischemic lesion was more extensive in their study. Therefore, how the reduction or elevation of afterload pressure affects the regional function of the ischemic myocardium is controversial. Although they did not quantitatively examine the effect of graded reduction or elevation of the mean AoP, they might have obtained the same results as we did if they had examined the effect of graded reduction of mean AoP. Furthermore, since the LVEDP was not controlled in their study, 12, 13 we must consider the effect of the change in preload when considering the data reported by Wyatt et al. 14

Global Ventricular and Regional Myocardial Function

In hearts without ischemia, CO and systolic shortening of the two regions increased with the reduction of Rp or mean AoP. On the other hand, in hearts with stenosis of the LCX branch, systolic shortening of the ischemic region increased with a small reduction of Rp or mean AoP, and decreased with their further reduction. At the same time, systolic shortening of the nonischemic region during ischemia tended to increase, compared with the extent of increase of systolic shortening in hearts without ischemia in the same region and at the same mean AoP (fig. 6B). As a net effect of systolic shortening in the two regions, the CO continued to increase with the reduction of Rp or mean AoP, even when ischemic myocardial function was extremely depressed. The relationship between CO and mean AoP during regional ischemia showed an almost parallel shift to the left and downward compared to the relationship in hearts without ischemia. These findings are similar to those of Elzinga and Westerhof, 20 which were obtained in an experiment using an isolated cat heart after a complete occlusion of a coronary arterial branch.

The trend of an increase in systolic shortening of the nonischemic region may be the result of interaction between nonischemic and ischemic regions. The ischemic region, by failing to shorten, may unload in the nonischemic region. Furthermore, systolic shortening of the nonischemic region during ischemia tended to increase, compared with shortening at the same region and for the same afterload pressure in the hearts without ischemia (fig. 6B). This change might be partially explained because of an increase in mean coronary blood flow of the nonconstricted branch.

The Relationship between the Coronary Blood Flow and the Regional Function

In the reports by Wyatt et al., 14 Downey, 3 Forrester et al., 4 and Waters et al., 5 coronary flow reduction from 100% to 60% of the control level produced no significant change in regional segmental mechanical function, and segmental performance was highly dependent on PP below a critical level between 50 and 65 mm Hg. In their studies, however, neither AoP nor preload was controlled. In fact, LVEDP was elevated to a higher value than the control value when ventricular function was depressed by the reduction of coronary blood flow in an open-chest dog. 1, 5 Therefore, we must consider the effect of preload change on the coronary blood flow–ventricular function relationship. 7 Furthermore, afterload pressure varied with a change in ventricular function, and the effect of the change in afterload pressure on the relationship between coronary blood flow and regional function during ischemia was not examined in their reports.

In this study, systolic shortening of the ischemic myocardium and CO decreased by 24 ± 6% and 15 ± 4%, respectively, when the mean blood flow of a coronary arterial branch was reduced to approximately 50% of the preischemic value at the control Rp. Within the range of the mean coronary blood flow from control to a 50% reduction, systolic shortening of the ischemic myocardium was highly dependent upon the afterload pressure; at less than 70% reduction of control, it was highly dependent upon coronary blood flow.

Clinical Implications

We examined the pure effect of afterload change on
the regional myocardial function in the presence of regional ischemia with constant heart rate and constant LVEDP, excluding the effect of such factors as the right ventricle, pericardium and neurohumoral factors.

We did not measure what level of LCx luminal narrowing was present to cause a 50% reduction in flow. However, the grade of the stenosis in our study may be similar to that of 85–90% luminal narrowing.21 Our data obtained from a stenosis that caused a 50% reduction in flow indicate that the regional function of the ischemic myocardium is aggravated by the reduction of mean AoP below approximately 70 mm Hg. Although we did not directly measure how the grade of the coronary stenosis affected the relationship between the afterload pressure and regional function of the ischemic myocardium, the different critical value of mean AoP could be obtained if the grade of the stenosis was different. The critical pressure would be higher, we believe, if the grade of the stenosis were more severe. Therefore, there would be many limitations for application of the present results to a clinical situation. However, our data do provide useful principles for the treatment of the patients with coronary stenosis. In afterload-reducing therapy for ischemic heart disease, we must consider the fact that the alteration of ischemic myocardium is more ischemic even when CO is increased with afterload reduction, because CO continues to increase with the reduction of mean AoP, even when regional function of ischemic myocardium is markedly depressed because of a decrease in coronary blood flow.

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