LABORATORY INVESTIGATION
VENTRICULAR PERFORMANCE

The effect of changes in afterload on systolic bulging

SHIGETAKA NOMA, M.D., ALAN D. ASKENASE, M.D., JAI B. AGARWAL, M.D., AND RICHARD H. HELFANT, M.D.

ABSTRACT It has been previously shown that after acute coronary occlusion, the extent of systolic bulging is dependent on preload and the function of the remote nonischemic myocardium is influenced by the motion of the ischemic myocardium as well as by the loading conditions. To examine the isolated effects of changing afterload on the movement of acutely ischemic and nonischemic myocardium, seven open-chest, anesthetized dogs were paced from the left atrium at a rate of 100 beats/min after crushing of the sinus node. The pulmonary artery was perfused artificially and the left ventricular end-diastolic pressure (LVEDP) was carefully controlled with a right heart bypass system. Twenty minutes after occlusion of the left anterior descending artery, the peak left ventricular pressure (LVP) was adjusted to three levels (70, 90, and 110 mm Hg) by blood withdrawal or aortic constriction, while the LVEDP was kept constant (8.3 ± 2.3 mm Hg). Segment length in the ischemic (IZ) and nonischemic zones (NZ) were measured with sonomicrometers and total, isovolumetric, and ejection systolic shortening (%ÂL) were calculated. Changes in left ventricular minor-axis diameter were measured with diameter crystals. Increasing the peak LVP increased the LVP both at aortic valve opening and closing. To keep the LVEDP constant as peak LVP was increased, the cardiac output had to be decreased (p < .0001). In the IZ, increasing the peak LVP increased isovolumetric bulge (−13.6 ± 3.4%, −14.4 ± 3.7%, and −15.0 ± 3.7% at LVP 70, 90, and 110 mm Hg, respectively, p < .00005) and decreased ejection %ÂL (4.8 ± 4.6%, 4.1 ± 4.3%, and 3.3 ± 4.4%, p < .05) so that total %ÂL was decreased (p < .001). In the NZ, increasing the peak LVP decreased both isovolumetric %ÂL (8.4 ± 2.7%, 7.1 ± 2.9% and 6.3 ± 2.8%, p < .00005) and ejection %ÂL (10.8 ± 6.5%, 9.6 ± 4.4%, and 8.8 ± 4.2%, p < .05) so total %ÂL was reduced (p < .00005). We conclude that increasing afterload increases the extent of the bulge in the ischemic zone and hypothesize that these changes are caused directly by an increase in wall tension. Increasing afterload also decreases shortening in nonischemic myocardium. Circulation 77, No. 1, 221–226, 1988.

ACUTE CORONARY OCCLUSION leads to characteristic changes in the contraction pattern of the ischemic myocardium.1, 2 With sonomicrometers, Theroux et al.3 demonstrated systolic bulging of ischemic tissue. Akaishi et al.4 showed how bulging occurred predominantly during isovolumetric shortening and that the slight inward motion of ischemic myocardium during ejection systole was passive. They further demonstrated that the extent of bulging depended on preload, and this dependence could be explained by the exponential shape of the tension-length relationship. However, the contraction pattern of nonischemic myocardium is also affected by acute coronary occlusion.

Several investigators have shown that the function of remote nonischemic myocardium is augmented after acute coronary occlusion.3, 5–7 Lew et al.8, 9 have shown that the isovolumetric bulging of ischemic myocardium is balanced by an increase in isovolumetric shortening of nonischemic myocardium if preload is kept constant. In addition, increasing the size of ischemic zone will increase the extent of nonischemic isovolumetric augmentation.10 If preload is allowed to increase after acute coronary occlusion, augmentation of nonischemic shortening will be due to increased ejection shortening via the Frank-Starling effect.11

In the work of Akaishi et al.4 and that of Lew et al.,8 the influence of preload on the movement of ischemic and nonischemic myocardium was demonstrated. In the present study we undertook the analysis of the influence of afterload on systolic bulging and augmentation of nonischemic myocardium. Right heart bypass was used to keep preload constant. Increasing afterload

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was found to increase systolic bulging and diminish isovolumetric and ejection nonischemic shortening.

Methods

Experimental preparation (figure 1). Seven mongrel dogs, weighing 24 to 32 kg, were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and ventilated with a mixture of oxygen and air by means of a Harvard respirator. Blood gases were monitored intermittently, and blood pH was maintained between 7.35 and 7.45. Standard electrocardiographic lead II was monitored continuously throughout each experiment. A thoracotomy was performed with a midline sternotomy and the heart was supported in a pericardial cradle. Both femoral arteries were cannulated with plastic tubes with a 3 mm internal diameter for withdrawing blood. Umbilical tape was placed around the descending aorta. A pacing electrode was sutured to the left atrial appendage. The sinus node was crushed by the injection of 1.0 ml of 40% formaldehyde and the heart was paced with a constant-current stimulator (MEDTRONIC 5325) at a rate of 100 beats/min throughout the experiment. A No. 5F catheter-tipped micromanometer (Millar Instruments) was introduced into the ascending aorta from the right femoral artery for monitoring arterial pressure. A second No. 5F catheter-tipped micromanometer (Millar Instruments) was inserted into the left ventricle from the apex for measurement of left ventricular pressure and dP/dt. The micromanometers were calibrated by placing their tips just under the surface of a beaker of saline at room temperature. Drift was minimized by leaving the catheters in the saline for at least 20 min. After being placed in the ascending aorta the two catheter-tipped micromanometers were matched against a fluid-filled catheter (No. 8F) monitored with a Statham P23Db transducer that was subsequently withdrawn.

A 1 cm portion of the left anterior descending artery was isolated before the first diagonal branch for coronary artery ligation. Two pairs of 2 mm ultrasonic segment length crystals were placed so that the first pair would be in the zone to be rendered ischemic after coronary artery occlusion (ischemic zone) and the second pair would be in the territory perfused by the left circumflex artery at the same circumferential level as the ischemic zone (nonischemic zone). Each pair of crystals was inserted into the inner third of the myocardium through small stab wounds perpendicular to the long axis of the left ventricle, approximately 10 mm apart. A pair of 5 mm ultrasonic diameter crystals was placed on the anterior and posterior endocardial surface through a small incision in the left ventricular apex to measure the left ventricular anterior-to-posterior minor-axis internal diameter, as described previously. Ultrasonic crystal motion was monitored with a standard imaging circuit (model 401, Schuessler and Associates). Positions of the crystals were verified at autopsy.

The right atrium was cannulated with a plastic tube with a 6 mm internal diameter that was connected to a 2 liter graduated cylinder that served as a reservoir. The main trunk of the pulmonary artery was cannulated with a plastic tube with the same internal diameter that was connected to the reservoir through a peristaltic roller pump (Travenol Laboratory Inc.). All venous return, including that from the coronary sinus, was drained to the reservoir and the pulmonary artery was perfused artificially with the pump. After each experiment, cardiac output at different times in the experiment was approximated by pumping saline through the bypass system at the same rates used during the experiment.

Experimental protocol. Propranolol (0.1 mg/kg) was injected at the start of the experiment to minimize reflex changes in sympathetic tone associated with an anesthetized state and acute interventions. Twenty minutes after initiation of modified right heart bypass, when hemodynamic variables and crystal

![FIGURE 1. Diagram of instrumentation. Ao = aorta; PA = pulmonary artery; RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; LAD = left anterior descending artery; LCX = left circumflex artery; IZ = ischemic zone; NZ = nonischemic zone; SVC = superior vena cava; IVC = inferior vena cava.](http://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.117.028642?journalCode=circ)
motions had stabilized, the left anterior descending artery was occluded. After 20 min, measurements were successively taken at peak left ventricular pressures (LVPs) of 70, 90, and 110 mm Hg, with left ventricular end-diastolic pressure (LVEDP) kept constant. To achieve an LVP of 70 mm Hg, blood withdrawal was required. To achieve an LVP of 110 mm Hg, constriction of the descending aorta by pulling in the umbilical tape was required. For an LVP of 90 mm Hg either constriction or blood withdrawal was required. As the LVP was increased, cardiac output had to be decreased to keep LVEDP constant.

**Data analysis and statistics.** Hemodynamic and crystal variables were recorded with the respirator turned off at the end of expiration and recorded on an Electronics for Medicine VR-16 recorder (Honeywell). Measurements were taken in the control state and at peak LVPs of 70, 90, and 110 mm Hg. After adjustment to a different LVP, recordings were made after all variables had stabilized, generally about 1 min.

End-diastole was defined as the point of the abrupt upstroke of left ventricular dP/dt during diastole. The onset of ejection was defined as the time when the left ventricular pressure surpassed the aortic pressure during systole. End-systole was defined as the time when the left ventricular pressure fell below the aortic pressure. According to these definitions, three myocardial segment lengths (mm) were measured in each cardiac cycle: the end-diastolic length (EDL), the length at the beginning of ejection (EjL), and the end-systolic length (EjS). Total percent systolic shortening (%ΔL), isovolumetric %ΔL, and ejection %ΔL were defined as:

\[
\text{Total } \%\Delta L = \frac{(EDL - ES)}{EDL} \times 100
\]

\[
\text{Isovolumetric } \%\Delta L = \frac{(EDL - EjL)}{EDL} \times 100
\]

\[
\text{Ejection } \%\Delta L = \frac{(EjL - ES)}{EDL} \times 100
\]

Thus the three variables were related:

Total %ΔL = isovolumetric %ΔL + ejection %ΔL

In addition, three left ventricular minor-axis diameters were measured in each cardiac cycle: end-diastolic diameter, the diameter at the beginning of the ejection, and end-systolic diameter.

Data are expressed as the mean ± SD. Paired groups of data were compared for significance by an analysis of variance for a one-factor experiment with repeated measurements.13 p < .05 was considered indicative of a significant difference.

**Results**

**Hemodynamics.** Hemodynamic data at the three levels of peak LVP are listed in table 1. Heart rate was kept constant at 100 beats/min throughout all the experiments. Increasing peak LVP increased LVP both at the time of the aortic valve opening and that of aortic valve closure. Peak left ventricular dP/dt increased slightly but significantly as peak LVP increased. Cardiac output approximated from the pumping rate was decreased as peak LVP was increased. Increasing peak LVP increased the duration of isovolumetric systole, while that of ejection was unchanged. As a result, the ratio of time in isovolumetric systole to ejection systole increased slightly (from 0.34 ± 0.07 to 0.40 ± 0.12, p < .05).

**Regional myocardial function and left ventricular diameter.** Figure 2 shows the tracings recorded from one experiment. The columns are, from the left, level 70, level 90, and level 110.

### Table 1

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>70 mm Hg</th>
<th>90 mm Hg</th>
<th>110 mm Hg</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak LVP (mm Hg)</td>
<td>72 ± 3</td>
<td>92 ± 1</td>
<td>111 ± 4</td>
<td>&lt;.00001</td>
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<tr>
<td>AVOP (mm Hg)</td>
<td>51 ± 5</td>
<td>72 ± 10</td>
<td>85 ± 9</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>AVCP (mm Hg)</td>
<td>57 ± 7</td>
<td>76 ± 4</td>
<td>97 ± 6</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>8.3 ± 2.4</td>
<td>8.4 ± 2.3</td>
<td>8.4 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>LV dp/dt (mm Hg/sec)</td>
<td>1142 ± 486</td>
<td>1328 ± 564</td>
<td>1571 ± 634</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>2.6 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Iso T (msec)</td>
<td>68 ± 17</td>
<td>74 ± 21</td>
<td>81 ± 24</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Eject T (msec)</td>
<td>197 ± 16</td>
<td>201 ± 15</td>
<td>202 ± 15</td>
<td>NS</td>
</tr>
</tbody>
</table>

AVOP = left ventricular pressure at the time of aortic valve opening; AVCP = left ventricular pressure at aortic valve closure; LV = left ventricular; CO = cardiac output approximated from pumping rate; Iso T = isovolumetric phase time; Eject T = ejection phase time.

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TABLE 2
Regional function and diameter

<table>
<thead>
<tr>
<th></th>
<th>70 mm Hg level</th>
<th>90 mm Hg level</th>
<th>110 mm Hg level</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic zone (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDL (mm)</td>
<td>16.39 ± 3.90</td>
<td>16.41 ± 3.95</td>
<td>16.43 ± 3.89</td>
<td>NS</td>
</tr>
<tr>
<td>EjL (mm)</td>
<td>18.58 ± 4.16</td>
<td>18.74 ± 4.19</td>
<td>18.87 ± 4.18</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>ESL (mm)</td>
<td>17.89 ± 4.41</td>
<td>18.14 ± 4.46</td>
<td>18.40 ± 4.52</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Total %ΔL</td>
<td>-8.84 ± 5.47</td>
<td>-10.27 ± 5.66</td>
<td>-11.76 ± 6.18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Isovolumetric %ΔL</td>
<td>-13.61 ± 3.36</td>
<td>-14.39 ± 3.68</td>
<td>-15.04 ± 3.68</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>Ejection %ΔL</td>
<td>4.77 ± 4.58</td>
<td>4.09 ± 4.31</td>
<td>3.30 ± 4.41</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Nonischemic zone (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDL (mm)</td>
<td>11.09 ± 1.37</td>
<td>11.13 ± 1.38</td>
<td>11.10 ± 1.38</td>
<td>NS</td>
</tr>
<tr>
<td>EjL (mm)</td>
<td>10.17 ± 1.53</td>
<td>10.37 ± 1.59</td>
<td>10.44 ± 1.58</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>ESL (mm)</td>
<td>8.94 ± 1.34</td>
<td>9.28 ± 1.37</td>
<td>9.44 ± 1.38</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>Total %ΔL</td>
<td>19.16 ± 5.16</td>
<td>16.69 ± 4.80</td>
<td>15.06 ± 4.83</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Isovolumetric %ΔL</td>
<td>8.40 ± 2.72</td>
<td>7.10 ± 2.91</td>
<td>6.27 ± 2.78</td>
<td>&lt;.0005</td>
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<tr>
<td>Ejection %ΔL</td>
<td>10.79 ± 5.27</td>
<td>9.59 ± 4.37</td>
<td>8.79 ± 4.19</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Diameter (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>25.97 ± 5.92</td>
<td>25.99 ± 5.94</td>
<td>26.03 ± 5.90</td>
<td>NS</td>
</tr>
<tr>
<td>EjD (mm)</td>
<td>24.57 ± 6.56</td>
<td>25.07 ± 6.76</td>
<td>25.31 ± 6.69</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>19.69 ± 6.49</td>
<td>20.77 ± 6.94</td>
<td>21.23 ± 6.94</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

EDL = end-diastolic length; EjL = length at the beginning of ejection; ESL = end-systolic length; EDD = end-diastolic diameter; EjD = diameter at beginning of ejection; ESD = end-systolic diameter.

90, and 110 mm Hg. Beneath the electrocardiogram is the tracing from the ischemic zone crystals. End-diastolic length remained constant throughout the experiment. As LVP increased both ischemic zone length at the beginning of ejection and end-systolic length increased, although length at the beginning of ejection increased to a lesser extent. The net result is that increasing LVP increased the magnitude of isovolumetric bulging, and the slope of the tracing during ejection systole became flatter. In the nonischemic zone, increasing peak LVP also increased both length at the beginning of ejection and end-systolic length, resulting in reduced isovolumetric and ejection %ΔL. A response to increasing peak LVP similar to that in the nonischemic zone was seen in left ventricular minor-axis diameter. Increasing LVP decreased both isovolumetric and ejection diameter shortening.

Table 2 lists the results of quantitative analysis of the effects of changes in afterload. End-diastolic length remained quite constant throughout the experiment both in the ischemic and nonischemic zones. In the ischemic zone, raising peak LVP increased both length at the beginning of ejection and end-systolic length. As a result total and isovolumetric %ΔL decreased (became more negative). Ejection %ΔL also decreased slightly but significantly. In the nonischemic zone increasing peak LVP increased both length at the beginning of ejection and end-systolic length diminishing total, isovolumetric, and ejection %ΔL. End-diastolic diameter was constant through-
The increase in LVP at the time of aortic valve closure leads to an increase in the length at end-systole. The result is increased bulging and decreased ejection shortening with higher LVPs. This response can be explained by changes in wall tension. Left ventricular minor-axis diameter lengthens as afterload is increased, resulting in increased wall tension as determined by Laplace's law. Tension was not directly calculated in the present study because the use of Laplace's law involves several assumptions that may not be valid in the regionally ischemic ventricle with acute changes in left ventricular pressure. Since wall tension at the beginning of ejection is usually higher than that at end-systole and the ischemic myocardium is on the steeper portion of the curve, increasing wall tension stretches the ischemic myocardium more at end-diastole than at the beginning of ejection. In addition, the increase in LVP at end-systole tends to be larger than that at the beginning of ejection. As a result, increasing peak LVP decreases the passive inward movement of the ischemic myocardium during ejection systole.

Nonischemic myocardial function was also affected by changing afterload. Although increasing afterload affected the isovolumetric and ejection shortening of nonischemic myocardium in the same direction as it affected that of the ischemic myocardium, that is, it decreased both, the causes are different because nonischemic myocardium does not move passively. Ejection shortening is decreased because the increase in segment length at end-systole is greater than the increase at the beginning of ejection. This is consistent with the results of experiments in vitro that showed that the extent of shortening in actively shortening myocardium is determined by afterload when contractility is constant. The reasons for the decrease in nonischemic isovolumetric shortening after coronary occlusion are less clear. Isovolumetric shortening in the intact left ventricle is generally of small magnitude. In open-chest preparations some regional differences have been described and the response to changes in preload is inconsistent. However, after coronary occlusion, nonischemic isovolumetric shortening consistently increases and is affected in a predictable way by changes in preload. As preload is increased, the extent of this augmented nonischemic isovolumetric shortening decreases as bulging decreases. The direction of changes is opposite and an interaction between the nonischemic and ischemic myocardium has been suggested. In the present study, a consistent effect on nonischemic isovolumetric shortening was seen with an increase in afterload, but the direction of change was the same as for ischemic bulging. Thus, it appears that the isovolumetric response of the nonischemic myocardium after coronary occlusion is not solely dependent on the extent of bulging but is influenced by afterload.

The effect of afterload on systolic bulging does not appear to be as great as that of preload. In our previous study, decreasing or increasing LVEDP by 4 mm Hg changed isovolumetric bulging by about 30%. In the present study, decreasing or increasing peak LVP by 20 mm Hg changed it by about 5%. As stated above, the mechanism by which increasing the LVEDP decreases bulging is a greater increase in segment length at end-systole than at the beginning of ejection, while increasing afterload increases bulging by increasing segment length at the beginning of ejection and at end-systole. Small changes in LVEDP cause relatively large changes in the length of the ischemic myocardium since at end-diastole the myocardium is on the flat portion of the tension-length curve. Aortic valve opening or closing occurs when the myocardium is on the steeper portion of the curve. Therefore, changes in the LVP at the beginning of ejection or at end-systole cannot change the length of the ischemic myocardium to any extent as large as changes in LVEDP.

Possible limitations. Our experimental preparation involved the use of open-chest anesthetized dogs. Although we cannot exclude some influence of pentobarbital anesthesia on myocardial function, a similar response of ischemic myocardium to changes in preload has been demonstrated in conscious dogs and in acute open-chest anesthetized dogs, suggesting validity of the open-chest preparation. In these experiments, we attempted to isolate the effect of changing peak LVP on the movement of acute ischemic myocardium. To keep LVEDP constant, it was necessary to decrease the cardiac output while LVP was increased. Since increasing LVP increases the end-systolic volume, cardiac output had to be decreased or the end-diastolic volume would have increased. Also, although the heart rate, LVEDP, and end-diastolic length were kept constant, left ventricular dP/dt increased with increasing peak LVP and the duration of isovolumetric systole increased. It has been shown that increasing the aortic diastolic pressure (the aortic pressure at the beginning of ejection) increases left ventricular dP/dt, while left ventricular dP/dt is theoretically independent of changes in afterload. It is also known that an increase in the aortic diastolic pressure prolongs the duration of isovolumetric systole without any change in contractility. We therefore believe that the changes in left ventricular dP/dt and the duration of
isovolumetric systole that we observed are secondary to the changes in aortic diastolic pressure and do not represent a change in contractility.

Clinical implications. Left ventricular function after acute coronary occlusion and the response of the left ventricle to pharmacologic or mechanical interventions is important prognostically. The present study and our previous work demonstrate the influence preload and afterload can have on regional function both of ischemic and nonischemic myocardium. Our results provide an experimental basis for afterload reduction in patients with acute myocardial infarction.

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