Reduction of Myocardial Infarct Size: Comparison Between Left Atrial and Left Ventricular Bypass

JOHN L. PENNOCK, M.D., WALTER E. PAE, JR., M.D., WILLIAM S. PIERCE, M.D., AND JOHN A. WALDHAUSEN, M.D.

SUMMARY A controlled study was undertaken to quantitate and compare the effect of left ventricular bypass (LVB) and left atrial bypass (LAB) on left ventricular infarct volume (LVIV). After baseline studies, the left anterior descending coronary artery in each of 30 mongrel dogs was ligated 1–1.5 cm from its origin. After baseline ischemic studies, control dogs (group 1 – 10 dogs), LAB dogs (group 2 – 10 dogs), and LVB dogs (group 3 – 10 dogs) were monitored for four hours. Final infarct size was determined by the nitroblue tetrazolium staining technique. Heart rate, mean arterial pressure, and total systemic flow (TSF) showed no significant difference between control and left heart bypass groups. In group 1, the LVIV was 27.7 ± 6.5 g/100 g left ventricle (LV). In group 2, left heart bypass (LHB) flow was 90 ± 4% of TSF. The pressure-time index (PTI) was 2845 ± 52 mm Hg-sec/min. The PTI demonstrated no significant difference from controls. In group 2, LVIV was 22.5 ± 6.0 g/100 g LV. LVIV was reduced 18.8% from controls (p < 0.08). In group 2, LHB was complete. Left ventricular decompression (group 3) resulted in a PTI of 328 ± 76 mm Hg-sec/min. The PTI was significantly different (p < 0.001) from groups 1 and 2. The LVIV was 12.6 ± 5.1 g/100 g LV. LVIV was reduced 54.5% from controls (p < 0.001) and 44.0% from group 2 (p < 0.001). These results suggest that LVB may be useful, not only in supporting the circulation in the patient with myocardial infarct and cardiogenic shock, but also in limiting infarct size.

CARDIOGENIC SHOCK due to pump failure has emerged as the primary cause of mortality in patients hospitalized for acute myocardial infarction. The intraaortic balloon can improve the circulatory status in 75% of patients with refractory cardiogenic shock. However, the mortality of patients treated by intraaortic balloon pumping is in the 90% range. Thus, a significant number of patients might benefit from a more aggressive form of mechanical circulatory assistance. Page and his associates demonstrated that patients who have sustained a myocardial infarction severe enough to cause cardiogenic shock had lost 40% or more of their left ventricular muscle mass, and concluded that cardiogenic shock is associated with extensive loss of left ventricular myocardium.

Despite measures to arrest the self-perpetuating circle of progressive, irreversible myocardial damage and cardiogenic shock, many patients die because too little viable myocardium remains. Cox and his associates have shown that the ischemic zone surrounding a necrotic infarction may continue to enlarge for as long as 10 hours after occlusion.

Circulatory assistance must perform a twofold function: first, it must aid the left ventricle in maintaining a reasonable perfusion pressure and cardiac output for vital organ function; second, it must increase myocardial oxygen supply or decrease myocardial oxygen demands in order to make oxygen available to injured cells and reduce the magnitude of myocardial injury. The counterpulsation mechanism of the intraaortic balloon effectively reduces the afterload of the left ventricle and myocardial oxygen consumption. However, to be beneficial, counterpulsation requires a certain level of left ventricular function. Other methods of circulatory assistance are needed that can take over a larger percentage of the left ventricular work than is possible with the intraaortic balloon. Left ventricular bypass has evolved experimentally as a useful form of circulatory assistance.

In this study we quantitated and compared the effect of left ventricular bypass and left atrial bypass on reducing left ventricular infarct volume.

Methods

Thirty mongrel dogs, weighing 19.4 ± 1.3 kg (SEM), were anesthetized with sodium pentobarbital (25 mg/kg), intubated with a cuffed endotracheal tube, and ventilated with 30% oxygen with a positive pressure ventilator. A median sternotomy was performed. An electromagnetic flowmeter was placed around the ascending aorta. A right femoral arterial catheter was advanced to the descending aorta for central aortic pressure monitoring and arterial blood sampling. The catheter was connected to a pressure transducer for continuous monitoring. A right femoral venous catheter was advanced into the inferior vena cava and connected to a pressure transducer for the measurement of central venous pressure. A short, rigid, wide-bore catheter was inserted into the left ventricular cavity through the left ventricular apex and

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FIGURE 1. Left atrial bypass preparation, group 2 dogs. Left atrium cannulated via the left atrial appendage.

connected to a transducer for the measurement of the left ventricular pressure. The ECG, central venous pressure, central aortic pressure, left ventricular pressure, and mean aortic flow were recorded on an eight-channel recorder.

All the dogs were prepared as described above, then divided into three groups. Group 1 comprised 10 control dogs. The 10 dogs in group 2 were additionally prepared with left atrial bypass (fig. 1). A #26F catheter was inserted into the left atrial appendage. Blood from the left atrium was drained by gravity into a specially designed open reservoir, a 1000 ml graduated cylinder with 10 ml increments. The reservoir allowed accurate quantitative addition or subtraction from the dog’s blood. The reservoir was primed with 500 ml uncrossmatched donor dog blood and 500 ml lactated Ringer’s solution. The remaining circuit consisted of a heat exchanger and a roller pump. Blood was returned via the left femoral artery using a #12F arterial catheter.

Finally, the 10 dogs in group 3 were prepared with left ventricular bypass (fig. 2). Blood from the left ventricle was drained by gravity into the same bypass circuitry described for group 2 dogs. In group 3 dogs, the #26F catheter was placed into the left ventricular cavity via a stab wound of the left ventricular apex. The catheter was secured with a pursestring suture of 0 silk suture.

FIGURE 3. Effect of two types of left heart bypass on infarct volume. Vertical bars indicate ± SEM.
After baseline studies, the left anterior descending coronary artery (LAD) of each dog was ligated 1.0–1.5 cm from its origin. After 15 minutes of ischemia, baseline ischemic studies were taken and bypass begun in dogs from groups 2 and 3. Control dogs (group 1), left atrial bypass dogs (group 2), and left ventricular bypass dogs (group 3) were monitored for 4 hours. After 4 hours, each experiment was ended and the dogs killed. The final infarct size was determined by the nitroblue tetrazolium (NBT) staining technique. At the conclusion of each experiment, the heart was excised, trimmed, and the left ventricular muscle mass weighed. The left ventricle was sliced carefully into slices 1 cm thick and incubated in NBT solution prepared by mixing one part 1 M phosphate buffer and eight parts distilled water at 37°C for 20–30 minutes by the methods of Nachlas and Shnita.4 Un-damaged muscle stained a deep blue color, and muscle unstained due to loss of intracellular dehydrogenases indicated muscle damage. Unstained muscle was excised, weighed, and related to 100 g of left ventricle (fig. 3). Thus, we estimated the final size of the myocardial infarction, in each animal.

The pressure time index (PTI) was established according to the following formula:

\[
\text{PTI} = \frac{\text{MDVP} \times \text{time index}}{100}
\]

where MDVP is the mean developed left ventricular pressure and time index is the duration of the ventricular pressure curves per minute.

The MDVP was obtained by planimetry of the area under the left ventricular pressure tracing, divided by the duration of the left ventricular pressure tracing, divided by the duration of the left ventricular pressure generated. Multiple curves were measured per experimental period and averaged.

We used the t test for paired data to test the significance of differences between mean values on all data. All values are expressed as mean ± SEM.

### Results

**Group 1 — Control**

Heart rate, mean arterial pressure, and total systemic flow (TSF) showed no significant difference between control group 1 and experimental groups 2 and 3 (table 1). The mean PTI 1 hour and 4 hours after ligation was 2715 ± 117 mm Hg-sec/min, and 2719 ± 114 mm Hg-sec/min, respectively, and showed no difference from group 2 animals (table 2). Mean PTIs did demonstrate a significant difference from group 3 dogs (p < 0.001). The left ventricular infarct volume (LVIV) for group 1 dogs was 27.7 ± 6.5 g/100 g left ventricle (LV) (table 3).

**Group 2 — Left Atrial Bypass**

The percentage left heart bypass flow rate was 90 ± 4% of TSF (table 4). The mean PTI 1 hour after ligation was 2800 ± 77 mm Hg-sec/min; 4 hours after ligation, the mean PTI was 2790 ± 52 mm Hg-sec/min. These values demonstrate no significant difference from controls. The LVIV for group 2 dogs was 22.5 ± 6.0 g/100 g LV (table 3). The LVIV was reduced 18.8% from controls (p < 0.08).

### Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before ligation</td>
<td>1 Hr. after ligation</td>
</tr>
<tr>
<td>1 Controls</td>
<td>113 ± 15</td>
<td>93 ± 3</td>
</tr>
<tr>
<td>2 Left atrial bypass</td>
<td>114 ± 11</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>3 Left ventricular bypass</td>
<td>122 ± 12</td>
<td>93 ± 6</td>
</tr>
</tbody>
</table>

### Table 2. Hemodynamic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Left ventricular peak pressure (mm Hg)</th>
<th>Pressure time index (mm Hg-sec/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>1 Hr. after ligation</td>
</tr>
<tr>
<td>1 Control</td>
<td>132 ± 9</td>
<td>122 ± 12</td>
</tr>
<tr>
<td>2 Left atrial bypass</td>
<td>138 ± 12</td>
<td>112 ± 8</td>
</tr>
<tr>
<td>3 Left ventricular bypass</td>
<td>140 ± 15</td>
<td>23 ± 4</td>
</tr>
</tbody>
</table>

* p values represent significant differences between control values and left heart bypass groups.
TABLE 3. Left Ventricular Infarct Volumes

<table>
<thead>
<tr>
<th>Group</th>
<th>Infarct weight in grams</th>
<th>Infarct weight in grams</th>
<th>Infarct weight per 100 grams left ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Control</td>
<td>84.9 ± 16.9</td>
<td>23.4 ± 6.4</td>
<td>27.7 ± 6.5</td>
</tr>
<tr>
<td>2 Left atrial bypass</td>
<td>82.5 ± 11.3</td>
<td>18.6 ± 5.5</td>
<td>22.5 ± 6.0</td>
</tr>
<tr>
<td>3 Left ventricular bypass</td>
<td>92.5 ± 11.7</td>
<td>12.0 ± 5.7</td>
<td>12.6 ± 5.1 (p &lt; 0.001) (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

*p values represent significant differences between control values and left heart bypass groups.

Group 3 — Left Ventricular Bypass

Left heart bypass was complete. Left ventricular decompression resulted in a mean PTI of 334 ± 86 mm Hg·sec/min at 1 hour after bypass, and a mean PTI of 328 ± 76 mm Hg·sec/min at 4 hours after bypass. TSF was via the left heart bypass circuit. No blood was ejected through the aortic valve. PTI was significantly different from group 1 and group 2 dogs (p < 0.001). LVIV was 12.6 ± 5.1 g/100 g L.V. LVIV was reduced 54.5% from controls (p < 0.001), and 44.0% from group 2 dogs (p < 0.001).

Discussion

Myocardial infarct area can be delineated using NBT. In the presence of a suitable substrate, dark blue formazan precipitate forms in myocardial fibers due to the reduction of the tetrazolium compound by preserved mitochondrial dehydrogenase. Thus, normal myocardium is rendered grossly dark blue or purple, while severely ischemic, infarcted, or scarred cardiac tissue is unstained. Feldman and his associates demonstrated that in nearly all instances, areas of nonstaining greater than 2 cm in diameter correspond to clinical and histological zones of infarction in dog hearts and postmortem preparations of human hearts. Roberts and his associates have shown a high degree of correlation of 99mTc-glucoheptonate scintigraphic infarct size with both predicted myocardial damage (epicardial ST-segment mapping) and determined infarct weight at autopsy using the NBT myocardial histochemical staining. These studies indicate that myocardium which is not NBT positive is non-salvageable.

Left ventricular bypass significantly reduces ischemic changes, detected by ST-segment mapping of the epicardium, after LAD ligation in dogs. However, the relationship varies for different volumes of myocardial muscle injury and ischemia. Once the myocardium sustains a severe ischemic insult, the intracardiac balloon suppresses ischemia and improves cardiovascular stability.

Although the value of reducing the pressure work of the heart is accepted, it is less clear how much benefit derives from reducing volume work (left atrial bypass), or how much additional benefit is gained by decompressing the left ventricle (left ventricular bypass). We studied the relationship between myocardial oxygen consumption and epicardial segment mapping (ST-segment improvement) in an ischemic preparation during left heart bypass. This study demonstrated that almost total bypass is necessary to benefit the injured heart significantly, and that the larger the infarct, the more important it is to increase the amount of bypass. Laks and associates recently confirmed this concept by demonstrating that left atrial-aortic bypass reduced the systolic left ventricular pressure, and reduced the PTI (p < 0.05), but did not reduce infarct size measured by ST-segment mapping in a large infarct model when instituted before occlusion or 20 minutes after occlusion.

The present study further verifies this concept. Ligation of the LAD 1.0–1.5 cm from its origin produces large infarctions, as shown in group 1. The results demonstrate the superiority of left ventricular bypass with decompression of the left ventricle in maximally salvaging myocardial muscle after coronary artery ligation in the dog. LVIV was reduced 54.5% from controls in group 3 dogs where indices of myocardial wall tension and intracardiac pressures were maximally reduced, and no external work was being performed by the left ventricle.

Table 4. Hemodynamic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Total systemic flow (l/min)</th>
<th>Bypass flow (%) total flow (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 1 Hr after ligation</td>
<td>4 Hr after ligation</td>
</tr>
<tr>
<td>1 Control</td>
<td>1.60 ± 0.16 1.55 ± 0.17 1.55 ± 0.18</td>
<td>0 0 0</td>
</tr>
<tr>
<td>2 Left atrial bypass</td>
<td>1.63 ± 0.40 1.66 ± 0.37 1.67 ± 0.36</td>
<td>0 1.47 ± 0.34 1.50 ± 0.30 (p &lt; 0.001) (p &lt; 0.001)</td>
</tr>
<tr>
<td>3 Left ventricular bypass</td>
<td>1.50 ± 0.16 1.55 ± 0.15 1.53 ± 0.12</td>
<td>0 1.55 ± 0.15 1.53 ± 0.12 (p &lt; 0.001) (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

*p values represent significant differences between control values and left heart bypass groups.
Reduction of the heart's oxygen utilization by left heart bypass has been studied by several groups. Dennis and his co-workers have shown that complete left heart bypass with left ventricular decompression is capable of reducing the myocardial oxygen consumption (MVO₂) to about 50% of control levels, and that lesser degrees of bypass reduce the oxygen utilization less markedly. Pierce and his associates demonstrated that maximum left atrial-to-aortic bypass, accounting for 85% of the total aortic flow, could reduce the MVO₂ by 22%. In contrast, they demonstrated that complete left ventricular-to-aortic bypass with left ventricular decompression was capable of reducing the MVO₂ by 47%. Jacobs and Hinglais demonstrated that even when total left heart bypass is achieved (left ventricular stroke volume equals zero), MVO₂ still depends on the volume-pressure conditions of the bypassed left ventricle. Left heart bypass reduces external work of the heart to zero and reduces wall tension, a major determinant of myocardial oxygen consumption.

Reduction of the extent of myocardial infarction by counterpulsation in dogs has been studied by Sugg and his associates, who demonstrated that counterpulsation used for a period of 2 hours immediately after circumflex ligation reduced the left ventricular infarct size to 15%, compared with 28% in control animals. If the use of counterpulsation was delayed for 24 hours after coronary ligation, the infarct size was reduced from 35% in the control group to only 28% in the assisted group. Zachowski recently evaluated the delay of onset of intraaortic balloon pumping, and duration of pumping on myocardial ischemia, and concluded that the balloon pump effectively reduced the severity and extent of acute ischemia when applied within 1–3 hours after the onset of ischemia and maintained for 3–6 hours. He also concluded that delay of initiation of counterpulsation reduces its potential effectiveness and a delay of 6 hours or more might be harmful. The difficulty in evaluating results of mechanical assistance arises from the difficult task of reproducing a standard infarct size in experimental animals. The effect can be substantially different between small infarctions and large infarctions.

Maroko and his associates demonstrated significant reductions in myocardial ischemia surrounding experimental infarctions following such interventions as propranolol infusions, elevations of arterial pressure with methoxamine, intraaortic balloon pumping, left ventricular decompression, glucose-insulin-potassium infusion, corticosteroid administration, and hyaluronidase. Most patients present clinically with cardiogenic shock complicating acute myocardial infarction several hours after their actual infarction. To determine if left ventricular bypass can significantly reduce infarct size several hours after the onset of an acute infarction will require further experimentation. Left heart bypass with left ventricular decompression may offer significantly better salvage of left ventricular myocardium than left atrial bypass without decompression in patients who remain hemodynamically unstable in spite of aggressive medical therapy and intraaortic balloon support.

References

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