The Influence of Combined Intra-aortic Balloon Counterpulsation and Hyperosmotic Mannitol on Regional Myocardial Blood Flow in Ischemic Myocardium in the Dog

JOHN T. WATSON, PH.D., DAVID E. FIXLER, M.D., MELVIN R. PLATT, M.D., BRENT B. NALL, G. KIMBLE JETT, AND JAMES T. WILLERSON, M.D.

SUMMARY We investigated the combined effectiveness of intra-aortic balloon counterpulsation and hyperosmotic mannitol (25%) on regional myocardial blood flow during acute coronary insufficiency. Cardiac output and paced heart rate were held constant in chloralose-anaesthetized dogs during right heart bypass. Acute coronary insufficiency was produced by ligation of the proximal left anterior descending coronary artery (LAD). Regional myocardial blood flow was measured using radioactive microspheres. Left ventricular end-diastolic pressure, mean aortic pressure, maximum left ventricular dp/dt, and hematocrit were unchanged by combined mannitol infusion and balloon pumping. Studies of combined treatment with balloon pumping and mannitol immediately after the second of two 13-minute consecutive reversible ligations of the LAD demonstrated that (1) collateral coronary blood flow increased 46% (P < 0.02) in ischemic myocardium compared with mannitol infusion alone during the first LAD ligation, and (2) collateral coronary blood flow increased 27% (P < 0.05) in ischemic myocardium compared with balloon pumping alone during the first LAD ligation. Studies in which combined treatment was delayed until 20 minutes after LAD ligation demonstrated that collateral coronary blood flow was elevated by 33% (P < 0.05) in ischemic myocardium compared to control studies in which balloon pumping alone had no effect. The results suggest that the increase in collateral coronary blood flow was in part a result of an increased transmural pressure gradient produced by balloon diastolic augmentation and the ability of mannitol to reduce coronary vascular resistance in ischemic myocardium.

IT PREVIOUSLY has been reported that hypertonic mannitol infused prior to and during acute myocardial ischemia increases total and collateral coronary blood flow in isolated perfused hearts.1 We have demonstrated that mannitol significantly increases total and collateral coronary blood flow in both anesthetized and unanesthetized, unsedated dogs.2 We also have shown that intra-aortic balloon pumping significantly increases collateral coronary blood flow in anesthetized dogs during acute coronary insufficiency, and that its effectiveness is dependent on the duration of ischemia prior to the initiation of balloon pumping.3 Clinically, intra-aortic balloon pumping alone has been effective in reversing cardiogenic shock in patients, but their long-term survival has been improved only modestly.4 The efficacy of intra-aortic balloon pumping might be further improved if it were used in conjunction with a pharmacological agent that increased collateral coronary blood flow to ischemic tissue. Since both hyperosmotic mannitol and balloon pumping improve collateral coronary blood flow in ischemic myocardium, the combined use of these interventions might increase collateral coronary blood flow above that observed with either alone. The purpose of this investigation was to determine the effectiveness of combined hypertonic mannitol and intra-aortic balloon pumping in modifying regional myocardial blood flow during acute coronary occlusion.

Methods

Adult dogs weighing 18–23 kg were anesthetized with α-chloralose (60 mg/kg, iv). Ventilation was provided through an endotracheal tube and a Harvard respirator using an oxygen gas mixture that maintained an arterial oxygen tension greater than 100 mm Hg. The chest was opened through a median sternotomy. The left anterior descending coronary artery (LAD) was mobilized just proximal to its first diagonal branch and a reversible ligation was placed around it. Venous return from the superior and inferior venae cavae was diverted from the right atrium to a bubble oxygenator (99% O₂ and 97% O₂ plus 3% CO₂) and heat exchanger (37 ± 1°C), and then returned through a Sarns model 5M6002 occlusive variable speed roller pump to the main pulmonary artery (right heart bypass) or left subclavian artery (total cardiopulmonary bypass). Thus, the rate of pumping into the pulmonary artery established a constant cardiac output for each dog. Ligatures placed on the pulmonary artery and the superior and inferior venae cavae completed the isolation of the right heart. Heart rate was kept constant in all experiments by atrial pacing. Proximal aortic pressure, left atrial pressure, and femoral artery pressure were measured through short, fluid-filled, vinyl catheters (inner diameter = 0.067 inch) connected to Statham P231a pressure transducers and were recorded on a multichannel Siemens direct writing re-
corder. Left ventricular (LV) pressure and the maximum rate of left ventricular pressure rise (LV dp/dt) were measured with a Millar pressure transducer catheter (PC-480) and amplifier (TCB104) (frequency response = 1,000 Hz).

Arterial blood gases, hematocrit, and osmolality (measured using Fiske osmometer and freezing point depression; range of error, ±3 mOsmol) were determined during each intervention.

To measure regional myocardial blood flow, radioactive microspheres 9 μm in diameter were used (133Ce, 85Sr, 47Sc) (3M Co.). Microspheres 15 μm in diameter (125I) were used for control determinations of flow in experiments in which four separate determinations of regional myocardial blood flow were made. At specific times 600,000–1,000,000 microspheres were injected into the left atrium with 5 ml of warm saline over a 10-second period. Starting immediately before the injection, blood was withdrawn at a constant rate of 10–15 ml/min with a constant speed Holter pump, and collected in counting vials from catheters tied into a femoral artery and the right internal mammary artery. During the microsphere injection, three 30-second reference blood samples were collected to ensure that all microsphere radioactivity had cleared the dead space of the collecting catheters and that none was being recirculated. At the end of each experiment the heart was removed and India ink (0.1 ml) was injected just distal to the proximal LAD ligature to outline the area of ischemia. This small volume of India ink was used to ensure that only the center of the ischemic area was removed and counted separately for radioactivity. The atria, epicardial fat, and coronary vessels were removed and the ventricles were separated into the right and left ventricular free walls, which were then further subdivided into subendocardial, subepicardial, and middle layers of approximately equal thickness. Separation of a middle layer clearly defined blood flow to the subendocardium and the subepicardium of the myocardium. The ventricular septum was subdivided into right, left, and middle portions. The anterior and posterior papillary muscles were excised from the free wall of the left ventricle. The heart and reference blood samples then were counted for radioactivity in a well gamma scintillation counter (Nuclear Chicago). Regional myocardial blood flow was determined by the method of Rudolph and Heymann, modified by use of different predetermined constants for differential spectrometry. Regional myocardial blood flow equals flow in the reference sample (averaged timed volumetric collection from the femoral artery and the right internal mammary artery) multiplied by the nuclide counts in the myocardial region of interest divided by nuclide counts in the reference sample. By collecting blood reference samples from arteries above and below the intracoronary balloon we made certain that the balloon was not occlusive and was not interfering with the distribution of the microspheres. Regional coronary blood flow was expressed in milliliters per minute per gram of tissue (0.4–1.0 ml/min per g). Blood flow per gram of tissue to the ischemic and nonischemic regions of the left ventricle was calculated from the sum of the blood flow to the subendocardium, subepicardium, papillary muscle, and middle layer divided by the total weight of the region.

In addition to regional myocardial blood flow, mean and phasic LV pressure, mean and phasic aortic pressure, mean left atrial pressure, and maximum LV dp/dt were measured before, during, and after each intervention. The experimental protocol for these investigations was as follows: The dog was placed on right heart bypass and the rate of pumping into the pulmonary artery was adjusted to provide a cardiac output that did not increase LV end-diastolic pressure above the normal range (<12 mm Hg) and to provide a mean aortic pressure of approximately 70–80 mm Hg. The cardiac output was kept constant for the remainder of the experiment. Control pressures were measured and either 125I or 133Ce was injected into the left atrium for control measurement of regional myocardial blood flow. Ten minutes later the proximal LAD was ligated for 13 minutes. At the end of that time, pressures and maximal LV dp/dt and regional myocardial blood flow were measured. The ligature around the LAD was released and the total cardiopulmonary bypass was reinstituted (blood returned through the subclavian artery) for a 30-minute recovery period, after which the dog was returned to right heart bypass. The proximal LAD again was ligated for 13 minutes and pressures, maximal LV dp/dt, and regional myocardial blood flow were measured at the close of this ischemic period. Results were calculated as percent change between the first and second 13 minutes of myocardial ischemia. This helped to eliminate dog-to-dog variation and allowed each dog to serve as its own control. Percent and absolute changes in regional myocardial blood flow were compared by t-test for paired differences and are considered statistically significant when P was less than 0.05. With this experimental protocol the following studies were performed.

GROUP 1

Eight experiments were performed without balloon pumping or mannitol infusion, using the protocol described above. These studies were considered to be timed control experiments and ensured that the passage of time had not altered regional myocardial blood flow or ventricular performance in dogs on right heart bypass during consecutive episodes of acute coronary occlusion.

GROUP 2

Six dogs were studied in which mannitol (25%) was infused intravenously at 7.6 ml/min starting immediately after the initial ligation of the LAD. Mannitol infusion was discontinued at the end of the first period of coronary occlusion and the serum osmolality was allowed to return toward its preligation control. Immediately after the second ligation of the LAD, mannitol again was infused intravenously and intra-aortic balloon counterpulsation (AVCO intra-aortic balloon pump) was begun. Measurements of regional myocardial blood flow and cardiac performance were made and then balloon pumping was discontinued and mannitol infusion was reduced to 3.8 ml/min to maintain a constant serum osmolality. A fourth measurement of pressure, LV dp/dt, and regional myocardial blood flow was made within 3 minutes after discontinuing balloon counterpulsation. In these studies the percent change in myocardial blood flow was calculated between the first and second period of myocardial ischemia and between the myocardial
blood flow determinations made with and without intra-aortic balloon pumping during the second period of myocardial ischemia.

GROUP 3

In seven dogs counterpulsation was begun immediately after the first ligation of the LAD and continued until regional myocardial blood flow had been determined. Immediately after the second ligation of the LAD balloon counterpulsation again was begun and mannitol was infused at 7.6 ml/min. Regional myocardial blood flow was determined and balloon pumping was discontinued.

GROUP 4

To test the effectiveness of intra-aortic balloon pumping if its institution was delayed after LAD ligation, balloon pumping in six dogs was begun 20 minutes after initiation of the ischemic period. Control flow was determined by injecting radioactive microspheres after the dog had been stable hemodynamically on right heart bypass. The LAD was ligated, and 20 minutes later regional myocardial blood flow was determined by injecting differently labeled radioactive microspheres. Balloon pumping then was begun with the LAD still ligated, and after 10 minutes of pumping regional myocardial blood flow was measured. Balloon pumping was discontinued immediately and 10 minutes later differently labeled radioactive microspheres were injected to measure post-balloon regional myocardial blood flow during coronary occlusion.

GROUP 5

Eight dogs were studied using the same protocol as that described above, except that 20 minutes after LAD ligation balloon pumping was combined with mannitol infused at 7.6 ml/min. After discontinuation of balloon pumping mannitol infusion was continued for 10 minutes at 3.8 ml/min to maintain a constant serum osmolality, and regional myocardial blood flow was measured once again.

In groups 4 and 5 changes in regional myocardial blood flow were expressed as percent change from the control measurement made 20 minutes after LAD ligation; therefore, each dog served as its own control.

Results

GROUP 1

Regional myocardial blood flow was unchanged in all regions studied when flow measured during the second LAD ligation was compared with flow during the first LAD ligation (Table 1).

Mean aortic pressure increased by 4 mm Hg and LV end-diastolic pressure increased by 2 mm Hg when the second LAD ligation was compared with the first, but these changes were not of statistical significance. There were no significant changes in mean aortic pressure, maximum LV dp/dt, diastolic aortic pressure, heart rate, hematocrit, and osmolality (Tables 1 and 2).

GROUP 2

Immediately after the second ligation of the LAD, intra-aortic balloon pumping was combined with intra-aortic balloon pumping and mannitol infusion alone during the first LAD ligation. In ischemic left ventricular tissue collateral coronary blood flow increased by 46 ± 13% (P < 0.02) over that observed during the initial period of coronary occlusion with mannitol infusion alone (Table 1). Subepicardial blood flow in the ischemic region increased by 32 ± 9% (P < 0.03); subendocardial blood flow in the same region tended to increase (36 ± 16%, P < 0.1) when compared with mannitol alone. The subendocardial to subepicardial blood flow ratio in ischemic myocardium was not altered by combined balloon pumping and mannitol (Table 1). Blood flow in nonischemic left ventricular myocardium also was increased by 59 ± 22% (P < 0.05) by balloon pumping and mannitol infusion when compared with mannitol infusion alone (Table 1). Both subepicardial and subendocardial blood flow in the nonischemic region increased significantly during balloon pumping and mannitol infusion (Table 1). Regional blood flow to the ventricular septum and right ventricle are not presented separately because in all studies flows to these regions were similar to flow measured in the nonischemic left ventricular region. Blood flow to the middle layer and papillary muscle of the ischemic and nonischemic regions of the left ventricle also are not presented separately because generally they were higher and paralleled blood flow to the subepicardium of the respective region.

Collateral coronary blood flow to the ischemic region decreased significantly (9 ± 3%, P < 0.05) when balloon pumping was discontinued 15 minutes after the onset of the second LAD ligation. In all other regions blood flow remained unchanged when balloon pumping was discontinued and the mannitol infusion was continued to maintain a constant serum osmolality.

Mean aortic pressure, LV end-diastolic pressure, maximum LV dp/dt, osmolality, and hematocrit were unchanged by combined treatment with mannitol and counterpulsation when compared with mannitol infusion alone (Table 2). A representative tracing of aortic blood pressure is presented in Figure 1.

GROUP 3

In these studies balloon pumping was combined with mannitol infusion immediately after the second LAD ligation and compared with the results of balloon pumping alone during the first LAD ligation. In ischemic myocardium collateral coronary blood flow was increased by 27 ± 10% (P < 0.05) by balloon pumping and mannitol infusion above that measured during the initial LAD occlusion with balloon pumping alone (Table 1). Ischemic subepicardial blood flow increased by 21 ± 8% (P < 0.05), whereas subendocardial blood flow was not significantly altered (27 ± 15%, P < 0.2) by combined balloon pumping and mannitol infusion. The subendocardial to subepicardial blood flow ratio in ischemic myocardium was not altered by balloon pumping and mannitol infusion (Table 1).

In nonischemic left ventricular tissue combined balloon pumping and mannitol increased regional blood flow by 37 ± 10% (P < 0.01) compared to balloon pumping alone. In nonischemic subendocardial and subepicardial myocardium balloon pumping and mannitol increased blood flow by 40 ± 11% (P < 0.01) and 35 ± 9% (P < 0.01), respectively, compared to balloon pumping alone (Table 1).
COMBINED COUNTERPULSATION AND MANNITOL/Wattone/a/. 509

Mean aortic pressure, LV pressure, LV end-diastolic pressure, LV maximum dp/dt, and hematocrit remained unchanged during combined treatment with balloon pumping and mannitol compared with balloon pumping alone (Table 2).

COMPARISON OF GROUPS 2 AND 3

The results obtained for groups 2 and 3 are summarized in Figure 2. Regional blood flow with balloon pumping and mannitol is compared in this figure, as a percent, to regional blood flow measured with balloon pumping alone or mannitol infusion alone. The comparison indicates that the combination of balloon pumping and mannitol during the second LAD ligation significantly increased blood flow in both ischemic and nonischemic left ventricular myocardium above and above that measured with balloon pumping alone or mannitol alone. After cessation of balloon pumping during the second LAD ligation and with continued mannitol infusion, blood flow to ischemic tissue fell significantly (Fig. 2, M) but was unaltered in nonischemic tissue.

GROUP 4

Balloon pumping alone, begun 20 minutes after LAD ligation, was ineffective in altering regional myocardial
blood flow in either ischemic or nonischemic myocardial tissue (Fig. 3 and Table 1). Similarly, balloon pumping alone did not significantly change any of the hemodynamic parameters measured except for systemic arterial diastolic pressure, which was significantly increased (Table 2).

**GROUP 5**

In ischemic myocardium the combination of 10 minutes of balloon pumping and mannitol infusion 20 minutes after LAD ligation increased collateral coronary blood flow by 33 ± 13% (P < 0.05) compared to flow measured before the combined treatment (Fig. 3 and Table 1). Ischemic subepicardial blood flow increased by 51 ± 18% (P < 0.03), and subendocardial blood flow tended to increase (63 ± 33%, P < 0.1) with 10 minutes of balloon pumping and mannitol after 20 minutes of acute coronary occlusion. The subendo-

**TABLE 2 Hemodynamic Parameters**

<table>
<thead>
<tr>
<th>Group 1 (n = 8) (CO = 1.35 ± 0.12)</th>
<th>MAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LV dp/dt (mm Hg/sec)</th>
<th>HR (beats/min)</th>
<th>Hematocrit (%)</th>
<th>Osmolality (mosmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>73 ± 5*</td>
<td>60 ± 3</td>
<td>7.7 ± 1</td>
<td>1921 ± 226</td>
<td>133 ± 7</td>
<td>30 ± 2</td>
<td>326 ± 12</td>
</tr>
<tr>
<td>LAD ligation 1</td>
<td>82 ± 6</td>
<td>70 ± 7</td>
<td>10 ± 1</td>
<td>1943 ± 195</td>
<td>134 ± 7</td>
<td>32 ± 2</td>
<td>324 ± 10</td>
</tr>
<tr>
<td>LAD ligation 2</td>
<td>86 ± 6</td>
<td>74 ± 8</td>
<td>12 ± 2</td>
<td>1950 ± 187</td>
<td>135 ± 6</td>
<td>35 ± 2</td>
<td>322 ± 8</td>
</tr>
</tbody>
</table>

**Group 2 (n = 6) (CO = 1.46 ± 0.11)**

| Control                          | 74 ± 3      | 60 ± 2      | 2.7 ± 0.7     | 4225 ± 516         | 116 ± 9       | 32 ± 3        | 296 ± 5            |
| LAD ligation 1 + mannitol        | 80 ± 3      | 65 ± 5      | 5.5 ± 0.5     | 4360 ± 1152        | 124 ± 10      | 31 ± 3        | 316 ± 5            |
| LAD ligation 2 + mannitol + 1ABP| 88 ± 4      | 103 ± 5†    | 5.3 ± 0.8     | 3930 ± 802         | 125 ± 11      | 30 ± 3        | 329 ± 5            |
| LAD ligation 2 + mannitol alone, 3| 79 ± 5      | 65 ± 6      | 4.9 ± 0.8     | 3450 ± 406         | 126 ± 11      | 30 ± 2        | 329 ± 6            |

**Group 3 (n = 7) (CO = 0.93 ± 0.08)**

| Control                          | 78 ± 3      | 68 ± 3      | 1.9 ± 0.3     | 2074 ± 117         | 144 ± 6       | 35 ± 3        | 306 ± 3            |
| LAD ligation 1 + 1ABP            | 83 ± 2      | 99 ± 3      | 2.7 ± 0.5     | 1957 ± 149         | 150 ± 7       | 34 ± 3        | 305 ± 4            |
| LAD ligation 2 + 1ABP + mannitol | 81 ± 3      | 95 ± 4      | 3.1 ± 0.8     | 2233 ± 129         | 158 ± 12      | 33 ± 3        | 329 ± 4            |

**Group 4 (n = 6) (CO = 1.15 ± 0.14)**

| Control                          | 76 ± 1      | 64 ± 2      | 3.5 ± 0.8     | 2208 ± 362         | 143 ± 9       | 37 ± 2        | 313 ± 7            |
| 20 min after LAD ligation        | 82 ± 3      | 73 ± 3      | 4.5 ± 0.6     | 2067 ± 263         | 145 ± 7       | 39 ± 2        | 311 ± 6            |
| 10 min IABP                      | 82 ± 2      | 99 ± 6      | 4.7 ± 1.0     | 1908 ± 243         | 141 ± 7       | 39 ± 1        | 310 ± 5            |
| Ischemia continued               | 80 ± 4      | 71 ± 4      | 4.4 ± 1.0     | 1908 ± 225         | 139 ± 7       | 39 ± 2        | 310 ± 5            |

**Group 5 (n = 8) (CO = 0.88 ± 0.04)**

| Control                          | 79 ± 3      | 65 ± 3      | 4.4 ± 0.7     | 1656 ± 115         | 123 ± 6       | 34 ± 2        | 307 ± 5            |
| 20 min after ligation            | 77 ± 3      | 64 ± 4      | 5.9 ± 0.4     | 1625 ± 67          | 131 ± 8       | 34 ± 2        | 310 ± 5            |
| 10 min IABP + mannitol           | 82 ± 3      | 100 ± 3     | 5.3 ± 0.5     | 1593 ± 94          | 126 ± 6       | 32 ± 2        | 330 ± 5            |
| Mannitol continued               | 70 ± 3      | 58 ± 4      | 5.0 ± 0.5     | 1562 ± 91          | 122 ± 6       | 32 ± 2        | 330 ± 5            |

MAP = mean aortic pressure; DAP = diastolic aortic pressure; LVEDP = left ventricular end-diastolic pressure; LV dp/dt = maximum rate of left ventricular pressure rise; HR = heart rate; CO = cardiac output (liters/min); n = number of experiments; LAD = left anterior descending coronary artery; IABP = intra-aortic balloon pumping.

*SE of the mean.
†Maximum DAP.

**FIGURE 1** Comparison of phasic aortic blood pressure (ABP) during mannitol infusion during the first ischemic period (I) with blood pressure measured during the second ischemic period when balloon pumping was combined with mannitol (BP + M) and when mannitol was continued to maintain constant osmolality (M). MAP = mean aortic pressure.

**FIGURE 2** Regional myocardial blood flow with balloon pumping and mannitol (BP + M) during the second ischemic period compared with balloon pumping alone (BP) and mannitol infusion alone (M) during the first ischemic period. Ischemic left ventricular tissue is shown in the upper panel and nonischemic left ventricular tissue in the lower panel. The combined treatment (BP + M) is also compared with regional myocardial blood flow after cessation of balloon pumping with continued mannitol infusion (M') during the second period. Asterisk (*) = P < 0.05; A = P < 0.02.
cardial to subepicardial blood flow ratio in ischemic myocardium was lowered after 20 minutes of LAD ligation and remained depressed after 10 minutes of combined balloon pumping and mannitol infusion and after an additional 10 minutes of ischemia without balloon pumping (Table 1).

In nonischemic myocardium balloon pumping and mannitol infusion increased coronary blood flow by 13 ± 4% (P < 0.02) compared to blood flow measured before combined treatment (Fig. 3). Blood flow was increased in the nonischemic subepicardium by 16 ± 5% (P < 0.02) and in the nonischemic subendocardium by 12 ± 5% (P < 0.05) (Table 1).

There was a fall in collateral coronary blood flow of 13 ± 5% (P < 0.05) in ischemic myocardium after cessation of balloon pumping. In nonischemic myocardium coronary blood flow remained elevated by 17 ± 5% (P < 0.02) (Fig. 3). Mean systemic pressure, LV end-diastolic pressure, maximum LV dp/dt, and hematocrit were not significantly altered during these studies (Table 2).

Discussion

Previously we have shown that intracoronary balloon pumping initiated before or immediately after ligation of the LAD significantly increases collateral coronary blood flow in ischemic myocardium. However, when balloon pumping was begun 20 minutes after ligation of the LAD it failed to increase myocardial blood flow. The factor(s) responsible for the failure of delayed balloon pumping to improve regional blood flow in ischemic myocardium have not yet been identified, but possibilities include an increase in vascular resistance resulting from cell swelling, a change in arterial or venous tone, an accumulation of interstitial myocardial fluid, and/or some other intrinsic myocardial alteration resulting in an increase in coronary artery resistance.

Our experience with hypertonic mannitol has demonstrated an increase in regional blood flow to ischemic and nonischemic myocardium in both awake and anesthetized animals. In our previous studies balloon pumping did increase coronary blood flow in ischemic tissue during most experimental conditions, but did not significantly change blood flow in nonischemic tissue. Therefore, it seemed possible that the combined use of intracoronary balloon pumping with a pharmacological agent such as hyperosmotic mannitol might further improve the distribution of regional myocardial blood flow during acute coronary occlusion and also might allow us to better understand the mechanism(s) responsible for the ineffectiveness of balloon pumping alone in redistributing coronary blood flow 20 minutes after LAD ligation. Two recent reports support our finding that 10 minutes of balloon pumping after 20 minutes of coronary occlusion may not alter regional blood flow in ischemic myocardium. Reneman et al. reported that 3 hours of counterpulsation after 5–15 minutes of LAD occlusion failed to alter collateral coronary blood flow in ischemic myocardium. Shaw et al. found that balloon pumping for 30 minutes after 1 hour of LAD ligation did not significantly increase blood flow in ischemic myocardium.

The results of the present studies indicate that in ischemic myocardium intracoronary balloon pumping combined with the intravenous infusion of hypertonic mannitol increases collateral coronary blood flow over and above the change effected by either intervention alone. This effect was observed when the combination was initiated either immediately, or delayed 20 minutes, after LAD ligation. The combination of balloon pumping and hypertonic mannitol also significantly increased coronary blood flow to the nonischemic region of the left ventricle. The increase in flow to this region effected by the combined interventions was greater than that noted with mannitol infusion alone (Table 1, group 2). Importantly, balloon pumping and mannitol infusion did not significantly change any aspect of ventricular performance apart from elevating diastolic arterial blood pressure (Table 2). Thus, the combined effect of intracoronary balloon counterpulsation and hyperosmotic mannitol primarily enhances regional myocardial blood flow during acute myocardial ischemia.

Regional myocardial blood flow significantly increased in the subepicardium of ischemic tissue during intracoronary balloon pumping and mannitol infusion in groups 2, 3, and 5 and also tended to increase in the subendocardium. Immediately or 10 minutes after discontinuation of balloon pumping, but with continuing mannitol infusion, regional myocardial blood flow fell significantly in ischemic myocardium, but remained elevated in nonischemic tissue. The mechanism responsible for this decrease in collateral coronary blood flow may have been the reduction in systemic arterial...
diastolic blood pressure that occurred after balloon pumping was discontinued.

Previously we have shown that both intra-aortic balloon pumping and external counterpulsation can significantly increase collateral coronary blood flow to ischemic myocardium, and primarily to the subepicardial region, when they are initiated immediately after LAD occlusion. This enhancement in collateral coronary blood flow could not be attributed to a change in mean aortic pressure, peak LV pressure, heart rate, and/or cardiac output, but was probably caused by an increased transmural pressure gradient across the myocardial wall resulting from diastolic arterial pressure augmentation.

The present data and our previous results suggest that the increase in regional myocardial blood flow in ischemic tissue noted in the current studies may have resulted from the ability of balloon pumping to increase the systemic arterial diastolic blood pressure and the effect of hyperosmotic mannitol to reduce coronary vascular resistance. The increase in nonischemic regional myocardial blood flow noted during the administration of mannitol presumably was not dependent upon the ability of mannitol to alter cell swelling, because cell swelling should not have occurred in these region(s). The transmembrane osmolality gradient produced by hyperosmotic mannitol may have a direct effect on vascular smooth muscle and/or may reduce endothelial and interstitial cell size even in nonswollen cells, thus reducing intravascular and extravascular resistance to flow. Whatever the mechanism(s), it appears that the efficacy of balloon pumping in redistributing coronary blood flow during acute myocardial occlusion is enhanced appreciably when used in combination with hypertonic mannitol.

Other investigators recently have reported on the combined effectiveness of intra-aortic balloon pumping and various pharmacological agents. Matloff et al. studied the combined effectiveness of balloon pumping and glucagon in a dog in which cardiogenic shock was produced by injecting mercury into the circumflex artery and the left anterior descending coronary arteries. They found that balloon pumping combined with glucagon significantly enhanced myocardial performance above that measured with either intervention alone. In 1973 Spotnitz et al. reported that the use of a massive bolus of propranolol in combination with balloon pumping decreased myocardial contractility and oxygen consumption while maintaining a normal cardiac output. Feola et al. demonstrated that phenylephrine combined with balloon pumping was more effective in decreasing S-T segment elevation during experimental myocardial ischemia than either intervention alone. Their results were confirmed by Clayman et al. Parmley et al. reported on the combined effect of external counterpulsation and nitroprusside. In clinical studies they found the combined use of these two modes of therapy, nitroprusside for systolic unloading and balloon pumping for diastolic arterial pressure augmentation, was more effective than either intervention alone.

Willerson et al. have shown that hypertonic mannitol can significantly reduce epicardial S-T segment elevation during acute myocardial ischemia. Other investigators have reported that both balloon pumping and external counterpulsation can significantly reduce epicardial S-T segment elevation in dogs during acute myocardial ischemia. Klener et al. have presented histological evidence of the ability of hypertonic mannitol to reduce infarct size after a 40-minute occlusion of the canine circumflex coronary artery. The results of the present study support the data obtained previously by others and suggest that the physiological significance of the increased regional myocardial blood flow produced by combining intra-aortic balloon pumping and mannitol infusion may be a reduction in tissue ischemia and infarct size within the region normally perfused by the occluded LAD.

In these studies microspheres 15 μm in diameter were used for preligation control measurement of blood flow in some studies requiring four different microspheres. Subendocardial to subepicardial blood flow ratios obtained with 15-μm microspheres have been reported to be higher than those obtained with 9-μm microspheres; therefore, no direct statistical comparisons of subendocardial to subepicardial blood flow ratios were made between preligation and postligation ratios (Table I).

In summary the results of the present studies demonstrate that the combined effectiveness of intra-aortic balloon counterpulsation and hypertonic mannitol in influencing regional myocardial blood flow to ischemic and nonischemic myocardium is greater than with either intervention alone. They also demonstrate that the failure of delayed intra-aortic counterpulsation to increase coronary blood flow to the ischemic region of the left ventricle may be partially corrected by the infusion of mannitol. The mechanism(s) responsible for the increased effectiveness of the combined regimen in influencing regional coronary blood flow during acute myocardial ischemia is presumably related to the ability of balloon counterpulsation to increase coronary artery pressure and to the ability of mannitol to reduce coronary vascular resistance. The data obtained from these studies suggest that the combined influence of these interventions deserves clinical evaluation.

Acknowledgments

We thank Robert Wiskera, Doug Huffines, Francis Tyler, Peggy Barnett, and James M. Wheeler for expert technical assistance, and Donna Place for secretarial assistance.

References

7. Rudolph AM, Heymann MA: Circulation of the fetus in utero; methods

SUMMARY To clarify the postulate that turbulence may produce ejection murmurs, point velocity and sound were measured in the ascending aorta of 13 subjects: six with normal aortic valves, six with aortic valvular disease, and one with a Björk-Shiley prosthetic aortic valve. Velocity was measured with a catheter-tip hot film anemometer probe, and sound was measured with a catheter-tip micromanometer. Ejection murmurs detected intra-arterially were always found to be associated with turbulent or highly disturbed flow. Conversely, in the absence of intra-arterial sound during ejection, only minor disturbances of flow were detected. A linear relation between the sound energy density and turbulent energy density was shown \( r = 0.92 \) and a linear relation between the acoustic power output (sound intensity) and turbulent power supply \( (r = 0.87) \) also was shown. Studies in vitro of sound and point velocity distal to a porcine valve inserted within a cast of the aorta, which permitted precise centering of the transducers along the axis of flow, confirmed these observations. When the power generated by the turbulence exceeded 3 ergs/sec per cm², the murmurs were audible at the chest wall. The clinical gradation of the intensity of the murmurs increased as the power of turbulence increased. In conclusion, in this study we have demonstrated a clear association between turbulent blood flow and systolic ejection murmurs.

TURBULENT blood flow has been postulated to be the cause of ejection murmurs, \(^1\) although alternate mechanisms for the origin of ejection murmurs have been proposed. \(^1\) Prominent among these is periodic vortex shedding of Aoelian tones. \(^2\) Even the question of the existence of turbulent flow in the human body has been a matter of differing opinion. However, studies with point velocity sensors in animals support the likelihood of its existence. \(^4\) \(^4\) Studies in humans, establish that turbulent flow occurs above the aortic valve under some circumstances in normal humans, \(^5\) \(^4\) and it occurs routinely in the presence of aortic valvular disease. \(^5\) The purpose of this investigation was to determine the role of turbulent blood flow in the production of ejection murmurs.

Methods

Thirteen subjects were studied during diagnostic cardiac catheterization. Six subjects had normally functioning aortic valves, six had aortic valvular disease, and one had a Björk-Shiley prosthetic aortic valve. The study was approved by appropriate human experimentation committees, and informed consent was obtained from each subject. All subjects received light sedation with diazepam (Valium), which was taken orally.

Instantaneous point velocity in the ascending aorta was measured with a catheter-tip hot film velocity probe, used in combination with a TSI-1050 constant temperature anemometer (Thermo-Systems). The dynamic frequency response of hot film probes has been stated by Clark \(^6\) to be

---

TURBULENT FLOW AND MURMURS/Sabbah and Stein

HANI N. SABBAH AND PAUL D. STEIN, M.D.

Turbulent Blood Flow in Humans

Its Primary Role in the Production of Ejection Murmurs

HANI N. SABBAH AND PAUL D. STEIN, M.D.

From the University of Oklahoma College of Medicine and the Veterans Administration Hospital, Oklahoma City, Oklahoma.

Supported in part by the Veterans Administration Research Service.

Address for reprint: Dr. Paul D. Stein, Veterans Administration Hospital, 921 Northeast 13th Street, Oklahoma City, Oklahoma 73104.

Received August 20, 1975; accepted for publication February 6, 1976.

The influence of combined intra-aortic balloon counterpulsation and hyperosmotic mannitol on regional myocardial blood flow in ischemic myocardium in the dog.
J T Watson, D E Fixler, M R Platt, B B Nall, G K Jett and J T Willerson

Circ Res. 1976;38:506-513
doi: 10.1161/01.RES.38.6.506

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/38/6/506

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/