Effect of a Mechanical vs a Pharmacologic Increase in Aortic Pressure on Coronary Blood Flow and Thrombolysis Induced by IV Administration of a Thrombolytic Agent*

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This study was designed to compare the effect of a mechanical vs a pharmacologic increase in BP on coronary artery blood flow and thrombolysis induced by IV administration of recombinant tissue plasminogen activator. We employed a canine model of coronary thrombosis induced by injection of radioactive blood clot in the left anterior descending coronary artery. Subsequently, all dogs underwent phlebotomy to decrease systolic BP to 75 mm Hg and this decreased coronary blood flow by 50%. BP was increased to 130 mm Hg by norepinephrine (NE) infusion or by inflation of a Fogarty catheter placed in the descending aorta. Interventions with NE or with a Fogarty balloon catheter increased coronary artery blood flow to similar values and rates of coronary thrombolysis were similar. However, cardiac output was significantly higher with NE. These results indicate coronary clot lysis is dependent on perfusion pressure and coronary blood flow, not cardiac output. (CHEST 1997; 111:449-53)

Key words: aortic pressure; recombinant tissue plasminogen activator; thrombolytic therapy

Abbreviations: CO=cardiac output; r=correlation coefficient; rtPA=recombinant tissue plasminogen activator

Several large clinical studies have demonstrated that thrombolytic therapy decreases mortality in patients with acute myocardial infarction. However, this therapeutic approach is not reported to affect mortality in the subset of patients with cardiogenic shock. The failure for thrombolytic therapy to improve mortality in these patients may be due to the systemic hypotension impairing delivery of the thrombolytic agent, thus decreasing thrombolytic efficacy. Although previous studies have investigated the effect of different drugs, dosing regimens, and adjunctive therapy on thrombolytic efficacy, few studies have systematically investigated how changes in physiologic parameters, such as systolic BP, diastolic BP, and cardiac output, influence thrombolysis. A recent canine study demonstrated that a moderate increase in a low systolic pressure, attained by using a norepinephrine infusion, enhanced the rate of coronary thrombolysis induced by intracoronary administration of recombinant tissue plasminogen activator (rtPA). While we postulated that the increased thrombolysis was due to the increase in coronary perfusion pressure, it is conceivable that norepinephrine itself may have influenced thrombolysis. For example, in the presence of clot, norepinephrine may affect the regional coronary vascular resistance and thus, for a given coronary perfusion pressure, the delivery of the thrombolytic agent to the thrombus. That is, for the same increase in systolic pressure produced mechanically or by norepinephrine infusion, the delivery of the thrombolytic agent and thus the rates of thrombolysis could be different. Finally, we and others have speculated on the role of cardiac output itself in influencing coronary thrombolysis.

The current study compares the effect of a mechanical vs a pharmacologic increase in a low systolic BP on left anterior descending artery blood flow and coronary thrombolysis. Because cardiac output changes in different directions with these interventions, we also investigated the effect of cardiac output itself on coronary thrombolysis.
Eight dogs (24 to 34 kg) were anesthetized with IV pentobarbital sodium (30 mg/kg) that was supplemented as required to maintain anesthesia. Their treatment conformed to the guidelines of the University of Manitoba Animal Care Committee. Each dog was mechanically ventilated in a right lateral decubitus position via an endotracheal tube with 100% O2 with a tidal volume of 20 mL/kg. The respiratory rate was adjusted to maintain PaCO2 between 25 and 45 mm Hg. Metabolic acidosis was treated with sodium bicarbonate to maintain arterial pH greater than 7.28. A catheter was inserted into the left carotid artery for measurement of BP and for the removal of 20 mL of blood for autologous clot formation. Blood, for gas analysis, was also removed via this catheter. IV lines were inserted into the right and left femoral and external jugular veins for infusion of norepinephrine, sodium bicarbonate, lidocaine, and for phlebotomy as required. A thermistor-tipped flow-directed pulmonary artery catheter was inserted via the left external jugular vein and was positioned in the proximal pulmonary artery for measurement of thermodilution cardiac output (CO) and pulmonary artery diastolic pressure. The proximal port of the pulmonary artery catheter was used for injection of saline solution boluses for CO determination (Columbus Instruments; Columbus, Ohio). ECG, lead II, was used to monitor rate and rhythm. Lidocaine was given as required for ventricular premature depolarization. A Fogarty catheter was placed in the descending aorta via the right femoral artery. Effective placement of this catheter was confirmed by demonstrating that balloon inflation reproducibly increased aortic pressure.

Following catheterization, all dogs received a 2-mL IV injection of pancuronium bromide (2 mg/mL). A 15-cm incision was made in the left fifth intercostal space to expose the heart. Positive end-expiratory pressure of 2 to 3 cm H2O was applied posthernoracotomy. An incision was made in the pericardium to expose the left main coronary artery. The left anterior descending coronary artery was cleaned by blunt dissection and a calibrated 8-mm outer diameter flow probe (Carolina Instruments; King, NC) was placed distally. Subsequently, a piece of corticelli tape was threaded underneath the left anterior descending artery to steady it during cannulation with a 20-g 1.25-inch IV placement catheter (Ethalon IV; Criticon Canada Inc; Markham, Ontario). Following cannulation, the catheter was supported by two small strips of Teflon felt (Medox Medicals Inc; Oak Glen, NY), one on either side of the catheter and secured to the pericardium. This catheter was used for injection of 0.3 g of radioactive clot. The flow probe was positioned as close to the tip of the catheter as possible. Measurement of left anterior descending artery blood flow before and after catheter placement demonstrated that the catheter did not affect the measured coronary blood flow. Figure 1 illustrates this preparation. Following intracoronary catheter placement, the dogs were allowed a 30-min stabilization period.

All catheters were connected to transducers (Statham P23 I.D.; Gould; Oxnard, Calif) that were leveled to the mid sternum. The ECG was continuously recorded throughout the experiment. The output from all transducers and the flow probe was displayed on a 12-channel oscillograph (Electronics for Medicine; PPG Biomedical Systems; Lenexa, Kan) with recorder.

Radioactive Autologous Blood Clot Preparation

Each technetium-99m sulfur colloid preparation was prepared as previously described.8–10

Protocol

After stabilization, baseline measurements (mean, systolic and diastolic BP, pulmonary artery diastolic pressure, heart rate, coronary artery blood flow, and CO) were taken. Subsequently, 0.3 g of radioactive autologous clot was injected into the left anterior descending coronary artery via the catheter and was flushed through the catheter with normal saline solution. After a 20-min stabilization period, postclot measurements were obtained. Subsequently, all dogs were phlebotomized to decrease their systolic aortic pressure to approximately 75 mm Hg. In each dog, the rate of coronary thrombolysis was determined during a 15-min interval of rtPA infusion when the systolic aortic pressure had been increased to 130 mm Hg via Fogarty catheter inflation or by norepinephrine infusion. After ensuring steady-state conditions (stable systolic BP of approximately 130 mm Hg), 0.25 mg/kg of rtPA was infused IV over 15 min and the rate of thrombolysis was assessed. Subsequently, the Fogarty catheter was deflated or the norepinephrine infusion was stopped and systolic BP rapidly decreased to approximately 75 mm Hg. Then after 15 min, the alternate treatment was begun to increase the systolic BP to approximately 130 mm Hg. After approximately 10 min, the same dose of rtPA was infused over 15 min and the rate of thrombolysis again determined. Each dog was employed as its own control to eliminate intergroup variability. The initial use of norepinephrine or Fogarty catheter inflation was alternated from dog to dog to control for the effects of time. Employing this protocol in a previous study,8 we were able to reproducibly assess the effects of an intervention on coronary thrombolysis.

Assessment of Coronary Thrombolysis

Monitoring of cardiac radioactivity was achieved with a mobile gamma camera (Picker Dayna IV; Picker International Canada Inc; Winnipeg, Manitoba), equipped with a parallel hole collimator, coupled to a mobile computer (Medical Data Systems A2; Medtronic of Canada Ltd; Richmond, British Columbia). Dynamic images were acquired in a 64×64-byte mode for 2.5 h at a rate of 60 s per frame. In each study, a region of interest was...
placed about the heart. To assess the rate of coronary thrombosis, a percent radioactivity vs time plot was generated. A marker was placed at the onset of clot lysis. A second marker was placed on the plot at an interval 15 min after the onset of clot lysis. A regression line that best fit the data points within this interval was generated. The slope of the line defined the rate of clot lysis during this interval.

Statistical Analysis

Hemodynamic parameters were analyzed for a change with clot by paired t test. To assess the effect of increased systolic BP on coronary thrombosis by norepinephrine infusion and Fogarty catheter inflation, the paired t test was employed. To assess the hemodynamic effects of norepinephrine infusion and catheter inflation, a two-way analysis of variance was performed. If a significant F value was obtained, Tukey's test was applied to determine if there was a difference between mean values.

RESULTS

Table 1 illustrates mean (±SE) values of hemodynamic effects of coronary thrombosis in all eight dogs. Note that following clot, systolic BP, pulmonary artery diastolic pressure, and heart rate remained constant and CO decreased (p<0.005).

Figure 2 depicts the effects of clot on blood flow in the left anterior descending coronary artery. Note that following injection of clot, mean left anterior descending coronary artery flow decreased 17% (p<0.01). The magnitude of this decrease indicates that total occlusion did not occur at the level of the flow probe and that either the injected blood clot migrated more distally into the artery or lodged proximally and subtotally occluded the artery. Since the blood clot is soft and injected through a small caliber catheter, we favor the former possibility.

Table 2 demonstrates mean (±SE) values before and during norepinephrine infusion as well as before and during Fogarty catheter inflation. Note that measured values were similar both before norepinephrine infusion and before Fogarty catheter inflation, indicating stability of the preparation over time.

As dictated by experimental design, systolic BPs increased to a similar level with both interventions. The values for aortic diastolic pressure are also depicted in Table 2. The diastolic aortic pressure was slightly higher during balloon inflation (12%, p<0.05). Note that CO was higher during norepinephrine infusion than prior to norepinephrine infusion (p<0.01). As well, CO was higher during norepinephrine infusion than during balloon inflation (p<0.01). Heart rate also differed in the same way (both p<0.01).

Figure 3 plots mean (±SE) values and illustrates the effect of a mechanical and pharmacologic increase in left anterior descending coronary artery inflow pressure on left anterior descending artery blood flow. Note that compared with hypotension (postphlebotomy), both interventions significantly increased flow (p<0.01). Also note that values for

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### Table 1—Hemodynamic Effects of Clot*

<table>
<thead>
<tr>
<th>Metric</th>
<th>Preclot</th>
<th>Postclot</th>
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<tbody>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>108±6</td>
<td>108±6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>90±8</td>
<td>91±7</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>4±0.6</td>
<td>3±1.0†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>136±11</td>
<td>129±10</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>2.5±1.9</td>
<td>2.0±0.1†</td>
</tr>
<tr>
<td>PA diastolic pressure, mm Hg</td>
<td>11±2</td>
<td>12±3</td>
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</tbody>
</table>

*#n=8; all values are mean±SE. RAP=right atrial pressure. †p<0.05 compared with precLOT. ‡p<0.005 compared with precLOT.

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### Table 2—Hemodynamic Effects of Treatment*

<table>
<thead>
<tr>
<th>Metric</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>BP, mm Hg</td>
<td>69±3</td>
<td>122±4†</td>
</tr>
<tr>
<td>Systolic</td>
<td>50±3</td>
<td>83±2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>10±1</td>
<td>11±1</td>
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<tr>
<td>RAP, mm Hg</td>
<td>3±0.4</td>
<td>2.3±0.6</td>
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<tr>
<td>CO, L/min</td>
<td>14±0.1</td>
<td>2.7±0.3†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>135±10</td>
<td>184±11†</td>
</tr>
<tr>
<td>SV, mL/beats</td>
<td>10±1</td>
<td>15±2</td>
</tr>
</tbody>
</table>

*PAP=pulmonary artery pressure; RAP=right atrial pressure; HR=heart rate; SV=stroke volume; NE=norepinephrine. †p<0.01 compared with pre-NE and pre-balloon. ‡p<0.01 compared with pre-NE and balloons inflation. p<0.05 compared with NE. §p<0.01 compared with NE.
left anterior descending coronary blood flow are similar with norepinephrine and Fogarty catheter inflation. 

Figure 4 plots mean (±SE) values and depicts the rates of coronary thrombolysis obtained during norepinephrine infusion and Fogarty catheter inflation. Rates of clot lysis were similar with both interventions. The correlation coefficients (r) obtained by linear regression analysis of the count-time coordinates obtained during the two 15-min intervals of rtPA infusion indicate that they are well described by a line. The mean (±SE) r values obtained during norepinephrine infusion and Fogarty catheter inflation were 0.98±0.004 and 0.98±0.0053, respectively. All r values were significant to at least p<0.001.

**DISCUSSION**

Our study compared left anterior descending coronary artery flows and rates of coronary thrombolysis when systolic BP was pharmacologically increased with norepinephrine infusion or mechanically increased by inflation of a Fogarty catheter in the descending aorta. Systolic BP increased to a similar value with both interventions. Corresponding to the similar systolic BPs, diastolic BPs increased and thus led to an increased and similar left anterior descending blood flow. At similar rates of coronary blood flow, rates of coronary thrombolysis were similar.

A recent study investigated the effects of phlebotomy-induced hypotension, and normotension subsequently achieved with norepinephrine infusion, on coronary thrombolysis induced by intracoronary administration of rtPA.\(^8\) Compared with the hypotensive condition, coronary thrombolysis increased when norepinephrine increased systolic BP to normal values. We postulated that the increase in coronary thrombolysis was most likely due to increased delivery of the thrombolytic agent to the thrombus due to increased left anterior descending artery flow. A subsequent canine study confirmed this hypothesis.\(^11\) Similarly, another recent study demonstrated that in the presence of moderate hypotension (systolic BP of 90 mm Hg), intra-aortic balloon counterpulsation increased aortic diastolic pressure and the rate of coronary thrombolysis induced by IV administration of rtPA.\(^12\)

Current and recent studies are predicted by physiologic parameters governing flow in totally and subtotally obstructed vessels. That is, since the aortic pressure is the coronary inflow pressure, in subtotally occluded vessels (Thrombolysis in Myocardial Infarction Trial, Phase I),\(^4\) coronary flow is proportional, at least over a given range, to the driving pressure and inversely proportional to the regional vascular resistance. Therefore, changes in aortic pressure should affect delivery of the thrombolytic agent and thus thrombolysis. Further, an increase in aortic and thus transmural coronary artery pressure could convert a totally obstructed coronary artery into one with subtotal obstruction, a condition that would decrease regional vascular resistance and enhance thrombolysis.

Even though there is not an obligatory increase in coronary artery flow when CO increases, we\(^8\) and others\(^3\) have considered the potential role of CO itself in influencing coronary thrombolysis. In the current study, while systolic BPs, left anterior descending artery blood flows, and thrombolysis were similar with norepinephrine and Fogarty catheter inflation, CO was much higher with norepinephrine.

**FIGURE 3.** The effect of norepinephrine (NE) infusion and Fogarty catheter inflation on blood flow in the left anterior descending (LAD) coronary artery.

**FIGURE 4.** The rates of coronary thrombolysis obtained with IV administration of rtPA during norepinephrine (NE) infusion and during Fogarty catheter inflation. Values are expressed as mean±SE. For discussion, see text.
Therefore, current results indicate that, independent from CO, it is the aortic pressure that influences coronary thrombolysis.

The current results demonstrate that systolic BPs, left anterior descending artery blood flows, and rates of thrombolysis were similar with norepinephrine and Fogarty catheter inflation. Aortic diastolic pressure was slightly lower during norepinephrine infusion than balloon inflation. It may be argued that norepinephrine may have been associated with slight coronary artery vasodilatation in view of the lower aortic diastolic pressure and similar left anterior descending artery blood flow. Nevertheless, at similar anterior descending artery blood flow, clot lysis was not significantly different (Fig 4).

Although thrombolytic therapy decreases mortality in most patients with acute myocardial infarction, this approach does not decrease mortality in patients with cardiogenic shock. The failure of thrombolytic therapy to decrease mortality in this subset of patients may be due to a low BP impairing the delivery of the thrombolytic agent to the thrombus. One retrospective clinical report described a decrease in thrombolytic efficacy with intracoronary streptokinase in patients with cardiogenic shock. As cited above, similar results are reported in recent canine studies characterized by systemic hypotension. In addition to decreased thrombolytic efficacy, it is possible that the discouraging survival rate for patients with cardiogenic shock treated with thrombolytic therapy may also be partially explained by high reocclusion rates.

While as cited above, we favor increased delivery of the thrombolytic agent mediated by an increase in aortic pressure as the explanation for our results, it is possible that the increase in left anterior descending artery blood flow washed out or diluted clotting factors in the vicinity of the thrombus, thus minimizing the incorporation of fibrin into the thrombus. Finally, it is conceivable that a pressure-mediated increase in coronary blood flow may have caused fragmentation and washout of thrombus. Although we consider these latter two possibilities unlikely, our data do not allow us to rule them out.

There are obvious differences between the model of coronary thrombosis employed in the current study and acute myocardial infarction that occurs clinically. For example, in the current study, coronary thrombosis was induced by employing exogenously produced clot delivered through an indwelling catheter. Also, there is no underlying vascular abnormality at the site of thrombus in our model. In addition, the systemic hypotension complicating acute myocardial infarction is not due to phlebotomy. Because of these factors, we recommend caution in human clinical investigations in application of our results.

Despite the shortcomings cited, we stress that the current study is the first (to our knowledge) to systematically investigate the effects of mechanical vs pharmacologic changes in BP on coronary blood flow and coronary thrombolysis. Current and recent results highlight the importance of ensuring an adequate BP when thrombolytic therapy is administered.

REFERENCES