Intraaortic Balloon Counterpulsation Enhances Coronary Thrombolysis Induced by Intravenous Administration of a Thrombolytic Agent

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Objectives. This study was designed to test the hypothesis that in the presence of moderate hypotension, intraaortic balloon counterpulsation would enhance coronary thrombolysis induced by intravenous administration of recombinant tissue-type plasminogen activator (rt-PA).

Background. Although many studies have confirmed the efficacy of thrombolytic therapy in acute myocardial infarction, few have systematically investigated the effects of alterations in aortic pressure on coronary thrombolysis, and none have previously investigated the effects of intraaortic balloon counterpulsation on thrombolysis.

Methods. The effects of intraaortic balloon counterpulsation on aortic pressure, coronary blood flow and coronary thrombolysis were studied in a canine model. Coronary thrombosis was induced in eight dogs by injection of radioactive blood clot through a catheter placed in the left anterior descending coronary artery.

Although numerous studies have investigated intravenous administration of thrombolytic agents in acute myocardial infarction (1-3), few have systematically investigated the effects of changes in physiologic variables on thrombolytic efficacy. A recent study demonstrated that a moderate increase in low aortic pressure produced by norepinephrine infusion enhanced thrombolysis induced by intracoronary administration of recombinant tissue-type plasminogen activator (rt-PA) (4). Although intuitively, one might predict that intraaortic balloon counterpulsation, by augmenting aortic diastolic pressure, would enhance coronary diastolic flow, this approach did not increase coronary flow distal to tight stenotic lesions when blood pressure was normal (5). Conversely, the effect of counterpulsation on coronary artery flow and thrombolysis in the presence of hypotension has not been investigated.

The current study tests the hypothesis that in the presence of moderate hypotension, intraaortic balloon counterpulsation will enhance the rate of coronary thrombolysis induced by intravenous administration of a thrombolytic agent.

Methods

Eight dogs (22 to 29 kg) were initially anesthetized with intravenous sodium pentobarbital (30 mg/kg body weight). After transfer to the laboratory, dogs were given a sufentanil infusion (200 μg dissolved in 30 ml of normal saline solution) to decrease systolic blood pressure to approximately 110 mm Hg. Subsequently, sodium pentobarbital was given as required to maintain anesthesia. Treatment conformed to the guidelines of the University of Manitoba Animal Care Committee. Each dog was mechanically ventilated in the right lateral decubitus position via an endotracheal tube with 100% oxygen with a tidal volume of 20 ml/kg. The respiratory rate was adjusted to maintain arterial partial pressure of carbon dioxide between 25 and 45 mm Hg. Metabolic acidosis was treated with sodium bicarbonate to

Subsequently, dogs underwent phlebotomy to decrease systolic aortic pressure to ~90 mm Hg. After phlebotomy, during a 15-min interval of intravenous administration of rt-PA, coronary thrombolysis and coronary flow were determined during and in the absence of counterpulsation.

Results. Intraaortic balloon counterpulsation significantly increased aortic diastolic pressure. Corresponding to the increase in pressure, intraaortic balloon counterpulsation significantly increased the rate of rt-PA-induced coronary thrombolysis. Although not statistically significant, peak diastolic coronary flow tended to increase with counterpulsation.

Conclusions. These results indicate that in the presence of moderate systemic hypotension, intraaortic balloon counterpulsation enhances the rate of rt-PA-induced coronary thrombolysis. (J Am Coll Cardiol 1994;23:794-8)
maintain arterial pH >7.28. A catheter was inserted into the left carotid artery for measurement of blood pressure and for the removal of 20 ml of blood for autologous clot formation. Blood for gas analysis was also removed through this catheter. Intravenous lines were inserted into the right and left femoral and external jugular veins for infusion of sodium bicarbonate and lidocaine and for phlebotomy as required. A thermistor-tipped flow-directed Swan-Ganz catheter was inserted through the left external jugular vein and positioned in the proximal pulmonary artery for measurement of thermodilution cardiac output, pulmonary artery pressure and pulmonary capillary wedge pressure. The proximal port of the Swan-Ganz catheter was used for injection of saline solution boluses for cardiac output determination (Columbus Instruments). The electrocardiogram (ECG), lead II, was used to monitor rate and rhythm. Lidocaine was given as required for ventricular premature depolarization. An intracoracic balloon catheter, 8.5F or 5F (intraaortic balloon pump model System 82, Datascence Corp.) was placed through the right femoral artery into the descending aorta. Effective placement of this catheter was confirmed by demonstrating that balloon inflation reproducibly increased diastolic pressure.

After catheterization, all dogs received a 2-ml intravenous injection of pancuronium bromide (2 mg/ml). A 15-cm incision was made in the left fifth intercostal space to expose the heart. Two to three centimeters of water-positive end-expiratory pressure was applied after thoracotomy. 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) was placed distally. Subsequently, a piece of Corticelli tape was threaded underneath the artery to steady it during cannulation with a 20-g, 1.0-in. (2.54-cm) intravenous placement catheter (Cathlon IV, Critikon Canada, Inc.). After cannulation, the catheter was supported by two small strips of Teflon felt (Medox Medicals, Inc.), 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 coronary blood flow before and after catheter placement demonstrated that the catheter did not affect the measured coronary flow. After intracoracic catheter placement, the dogs were allowed a 30-min stabilization period.

All catheters were connected to Statham P23 I.D. transducers that were level to the midsternum. The ECG was continuously recorded throughout the experiment. The output from all transducers and the flow probe was displayed on a 12-channel Electronics for Medicine oscillograph with recorder.

Radioactive autologous blood clot preparation. Each technetium-99m (99mTc) sulfur colloid preparation was prepared by boiling 3.0 ml of 1 N hydrochloric acid, 3.0 ml of sodium thiosulfate pentahydrate and 10.0 to 11.0 GBq of 99mTc pertechnetate in 9.0 ml of saline solution for 3.5 min. After ice bath cooling for 5 min, 0.3 ml of human serum albumin and 8.0 ml of phosphate buffer were added. The purity of the 99mTc sulfur colloid preparations was determined to be 98.4 ± 0.3% by instant thin layer chromatography using methyl ethyl ketone as the solvent.

Technetium-99m sulfur colloid was chosen to label the clot because of its known affinity for fibrin strands and because the colloidal particles when released as a result of clot lysis are rapidly cleared by the reticuloendothelial system (serum half-life ~2 min), making correction for blood background radioactivity unnecessary (6,7).

To prepare the 99mTc sulfur colloid–labeled clot, 20 ml of blood from the dog was drawn in a 30-ml syringe. Approximately 130 MBq of 99mTc sulfur colloid (0.4 ml) was added to the syringe of blood. The syringe was capped and turned end over end 30 times to ensure thorough mixing of the 99mTc sulfur colloid in the blood. Clotting of the blood was done by simultaneously dripping the radiolabeled blood and 1,250 U (1.25 ml) of thrombin into a plastic cup 5 cm in diameter. The mixture was allowed to stand until the clot formed assumed a gelatinlike consistency, a process that takes approximately 1.5 h. Excess fluid was decanted and discarded. The clot was cut to yield a small piece of approximately 0.3 g containing 4.0 to 5.0 MBq of 99mTc sulfur colloid. The small piece of clot was placed in a 5-ml syringe, and 2 ml of saline solution was drawn into the syringe to facilitate injection of the clot into the coronary artery.

Protocol. After stabilization, baseline measurements (mean, systolic and diastolic blood pressures, pulmonary capillary wedge pressure, heart rate, coronary artery flow and cardiac output) were taken. Subsequently, 0.3 g of radioactive autologous clot was injected into the left anterior descending coronary artery through the catheter. The clot was injected and flushed through the catheter with normal saline solution. After a 20-min stabilization period, post-clot measurements were obtained. Subsequently, all dogs underwent phlebotomy to decrease systolic aortic pressure to approximately 90 mm Hg. After the adjustment in aortic pressure, in each dog the rate of coronary thrombolysis was determined during rt-PA infusion with and without intraaortic balloon counterpulsation. To control for time, the order of measurements was alternated. For example, in those dogs where rate of thrombolysis was initially determined during counterpulsation, after ensuring steady state conditions, 0.25 mg/kg of rt-PA was infused intravenously for 15-min, and the rate of thrombolysis was assessed. Subsequently, the counterpulsation was stopped. Then, after ~15 min the same dose of rt-PA was infused for 15 min. and the rate of thrombolysis was again determined. Each dog was used as its own control to eliminate intergroup variability. We used this protocol in a previous study (7) and were able to reproducibly assess the effects of intervention on coronary thrombolysis.

Assessment of coronary thrombolysis. Monitoring of cardiac radioactivity was achieved with a Picker Dayna IV
mobile gamma camera (Picker International Canada, Inc.) equipped with a parallel hole collimator coupled to a Medical Data Systems A2 mobile computer (Medtronic of Canada Ltd.). Dynamic images were acquired in a 64 × 64-byte mode for 2.0 h at a rate of 60 s/frame. In each study a region of interest was placed about the heart. The heart was imaged with an anteroposterior camera position to ensure that there was no overlap between the heart and liver or spleen. To assess the rate of coronary thrombolysis, a percent radioactivity versus 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 of 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 variables were analyzed for change with clot and phlebotomy by one-way analysis of variance. If a significant F value was obtained, the Student-Newman-Keuls test was applied to determine which means differed. To assess the effect of counterpulsation and rt-PA on hemodynamic variables, rate of coronary thrombolysis and coronary blood flow, a paired t test was used.

Results

Table 1 displays the mean values ± SE and illustrates the hemodynamic effects of coronary thrombus and phlebotomy in all eight dogs. After clot, cardiac output decreased, and pulmonary capillary wedge pressure, blood pressure and heart rate remained constant. Both cardiac output and blood pressure decreased with phlebotomy.

The peak diastolic aortic pressure increased in each dog with intraaortic balloon counterpulsation, and the mean change was 14 mm Hg (p < 0.01). The remaining hemodynamic variables remained constant.

Figure 1 plots individual data for peak systolic and peak diastolic flows in the presence and absence of intraaortic balloon counterpulsation. In six of seven dogs, peak diastolic flow increased with counterpulsation (p < 0.1). Mean flow did not change, and systolic flow decreased in five of seven dogs.

Figure 2 demonstrates that in each dog intraaortic balloon counterpulsation increased (p < 0.025) the rate of clot lysis. The relative increase in the rate of clot lysis with counterpulsation is indicated in each graph. This increase was quite variable between dogs, and comparatively small increases occurred in two dogs (9% and 22%). The mean relative increase in rate of clot lysis with counterpulsation was 83%. During rt-PA administration the rate of lysis is constant.

The correlation coefficient (r) obtained by linear regression analysis of the count-time coordinates for each of the 15-min drug infusion intervals indicates that during both intervals, the count-time coordinates were described by a line. The mean r values in the presence and absence of intraaortic balloon counterpulsation were 0.97 and 0.90, respectively. All r values were significant to at least p < 0.001. Before rt-PA infusion, the initial slope of the time-activity curve was flat, indicating trivial lysis.

Figure 1. Effects of intraaortic balloon counterpulsation (IABC) on peak systolic (left) and peak diastolic (right) coronary blood flow. See text for discussion.
Although peak diastolic flow increased in six of seven dogs with intraaortic balloon counterpulsation, because of large variability among dogs, there was no correlation between diastolic flow and rate of lysis.

**Discussion**

Our study investigated the effects of intraaortic balloon counterpulsation on coronary artery flow and coronary thrombolysis induced by intravenous administration of rt-PA. We demonstrated that although not significant, peak diastolic aortic flow tended to increase with intraaortic balloon counterpulsation. Most important, intraaortic balloon counterpulsation enhanced the rate of rt-PA-induced thrombolysis. However, we emphasize that the effect of counterpulsation on rt-PA-induced thrombolysis was quite variable, and in several dogs the relative increase in rate of lysis was comparatively small (Fig. 2).

Previous canine study. A recent canine study (4) investigated the effect of hypotension induced by phlebotomy and normotension produced by norepinephrine on coronary thrombolysis induced by intracoronary administration of rt-PA. Compared with the hypotensive condition, coronary thrombolysis increased when norepinephrine increased aor-
tic pressure. We postulated that the enhanced thrombolysis was due to increased delivery mediated by the higher pressure or by a direct mechanical effect, or both.

Potential mechanisms. In the current study, intraaortic balloon counterpulsation enhanced clot lysis. The mechanism of this effect may be related to two possibilities. Intraaortic balloon counterpulsation may have increased delivery of rt-PA to the clot by augmenting diastolic blood flow. Alternatively, the increased diastolic aortic pressure produced by counterpulsation may have mechanically fragmented the clot, thus providing a greater surface for rt-PA binding and thrombolysis. Fragmentation of upstream clot with distal embolization and no thrombolytic effect of rt-PA would not change the amount of radioactivity in the heart and thus would not be construed as thrombolysis by our method.

Methodology. During the two 15-min treatment intervals (i.e., the presence or absence of intraaortic balloon counterpulsation), the rate of lysis was constant, as signified by essentially linear time-activity curves. We do not believe that our findings are due to an artifact of changing rates of rt-PA-induced thrombolysis because our treatment intervals were short and were applied in alternating order in subsequent dogs. Furthermore, other work using the same model has demonstrated that only over a much longer treatment interval did the rate of lysis change (8). We did not have a control group that had no rt-PA treatment. We do not consider that our findings could be due to changing rates of spontaneous lysis because in this model if a thrombolytic agent is not used, the rate of lysis is trivial and is constant for ≥90 min (9). Alternating our treatment intervals also prevented systematic error, arising from any residual background activity from the adjacent pulmonary vasculature (6,7) or potential scatter from distant structures, such as the liver, from affecting our conclusions.

Other studies using intraaortic balloon counterpulsation. Previous clinical and experimental studies have failed to document an increase in coronary blood flow with intraaortic balloon counterpulsation. For example, Gewirtz et al. (5) reported that in normotensive pigs, intraaortic balloon counterpulsation did not increase coronary flow distal to permanent, tight stenotic lesions. In a previous study of patients with coronary artery disease (10), regional coronary flows did not increase with intraaortic balloon counterpulsation. Kern et al. (11) assessed the effects of intraaortic balloon counterpulsation on coronary flow velocity before and after angioplasty. Before angioplasty, the velocity of blood flow distal to the stenosis was unaffected by counterpulsation. However, angioplasty itself increased the distal velocity of blood flow, and after angioplasty counterpulsation further increased distal diastolic flow velocity. Peak systolic flow velocity was not increased with intraaortic balloon counterpulsation.

Cardiogenic shock. Although large clinical studies (2,3) have demonstrated that intravenous thrombolytic therapy decreases mortality in patients with acute myocardial infarction in relatively stable condition, this approach is not reported (12) to affect mortality in patients with cardiogenic shock. Conceivably, the failure of thrombolytic therapy to decrease mortality in these patients is due at least in part to low aortic pressure that decreases thrombolytic efficacy. Recent (4) and current results support this hypothesis.

Limitations of the model. There are obvious differences between the model of coronary thrombosis used in the current study and acute myocardial infarction complicated by hypotension that occurs clinically. Accordingly, caution should be used in extrapolating these results to the clinical setting.

We acknowledge the expert technical assistance of Michael Mass, CCP, Chris McCudden, CCP, Todd Koga, CCP and Dave Smith, CCP in carrying out this study.

References