Arterial Diastolic Pressure Augmentation by Intra-aortic Balloon Counterpulsation Enhances the Onset of Coronary Artery Reperfusion by Thrombolytic Therapy

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Background The early establishment of infarct artery reperfusion by intravenous thrombolytic therapy has improved survival after acute myocardial infarction. Investigations of reperfusion have focused on the effects of specific thrombolytic agents, anticoagulation, and platelet inhibition. However, little attention has been given to the relation of arterial blood pressure to thrombolysis, a factor that probably affects thrombolytic agent delivery to the obstructing thrombus.

Methods and Results The effect of arterial diastolic pressure augmentation by intra-aortic balloon counterpulsation (IABP) on reperfusion after intravenous thrombolytic therapy was studied in a canine model. A critical left anterior descending coronary artery stenosis was created by an occluder. Acute thrombosis immediately proximal to the occluder was formed by local injection of a blood and thrombin mixture into a segment of the artery that had intimal damage (groups 1 through 3). Continuous coronary blood flow velocity was measured by an epicardial Doppler probe. Group 1 (n=7) served as control. Group 2 (n=6) received an intravenous, front-loaded recombinant tissue-type plasminogen activator (tPA) regimen (1.25 mg/kg total dose, 15% as bolus, 50% in the first 30 minutes, and 35% for the following 60 minutes). Group 3 (n=6) received the same tPA regimen with IABP beginning at the start of tPA administration. Coronary blood flow velocity, arterial pressure, and heart rate were observed for 150 minutes after the start of thrombolytic therapy. Five animals did not undergo coronary thrombosis (group 4) and had coronary blood flow velocity determined before and after IABP at baseline and after creation of critical stenosis. Mean systolic arterial blood pressure and heart rate were not statistically different between groups. Peak augmented diastolic pressure by IABP was 97.9±1.3% of systolic pressure in group 3 dogs. Spontaneous reperfusion did not occur in any group 1 dogs. All animals treated with tPA reperfused. Reperfusion occurred in group 3 (13.1±2.1 minutes) earlier than in group 2 (39.2±9.4 minutes, P=.02). Overall duration of arterial patency did not differ between group 2 (81.4±16.6 minutes) and group 3 (94.9±15.3 minutes, P=.52). Reocclusions occurred with similar frequency (P=.85) in groups 2 and 3. In group 4, IABP did not increase baseline coronary blood flow velocity.

Conclusions This study demonstrates that augmentation of diastolic arterial pressure by IABP enhances thrombolysis, leading to faster reperfusion. This effect appears to be unrelated to an increase in coronary blood flow and may be due to an effect of the augmented diastolic blood pressure wave on the obstructing thrombus. These findings suggest that the time to reperfusion by tPA may be blood pressure dependent. The relation of arterial blood pressure to successful thrombolysis may have important implications for future treatment strategies for myocardial infarction. (Circulation. 1994;89:361-365.)

Key Words • thrombolysis • thrombosis • circulation • blood pressure • plasminogen activators

The restoration of coronary blood flow by intravenous thrombolytic therapy leads to improved survival in acute myocardial infarction. It has been demonstrated that the greatest survival and myocardial salvage occur with the establishment of early and sustained infarct artery patency. Therefore, strategies to enhance reperfusion by thrombolytic therapy and prevent reocclusion have been investigated. These studies have focused on the effects of platelet and coagulation pathway inhibition. Furthermore, much interest has been stimulated by the findings of enhanced reperfusion by novel dosing of thrombolytic agents. However, little attention has been given to the potential influence of arterial pressure in determining reperfusion. In a canine model in which a radiolabeled autologous clot was injected into the coronary artery, Prewitt et al demonstrated that marked hypotension impaired thrombolysis by recombinant tissue-type plasminogen activator (tPA). Evidence from several mortality trials supports an important relation between hemodynamics and successful thrombolysis. In addition, animal studies of thrombolytic therapy for pulmonary embolism support a direct relation of cardiac output to thrombolysis.

Based on the principle that the delivery of thrombolytic agents to the obstructing arterial thrombus is directly related to the arterial blood pressure, the effect of diastolic pressure augmentation on coronary artery reperfusion and reocclusion after intravenous thrombolytic therapy was investigated. The model used incorporated a critical coronary stenosis (P.A.G., manuscript submitted). Diastolic pressure was augmented by an intra-aortic balloon counterpulsation (IABP) device.
The effects of intra-aortic balloon pumping on coronary blood flow are controversial.\(^\text{11}\) However, we hypothesized that the augmentation of diastolic pressure, either by increasing coronary flow or creating a second enhanced arterial wave per cardiac cycle, could affect the obstructing thrombus and facilitate reperfusion by intravenous thrombolytic therapy. If arterial blood pressure directly effects the restoration of coronary blood flow, this finding would have important implications for future treatment strategies.

**Methods**

This study was approved by The Institutional Animal Care and Use Committee and conforms with The Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Twenty-four adult, male mongrel dogs (19 to 26 kg) were anesthetized with intravenous sodium pentobarbital and then ventilated with an Ohio anesthesia-ventilator pump with an oxygen flow rate of 2 L/min. Anesthesia was maintained with isoflurane, 2\% initially and 0.5\% maintenance thereafter. Arterial blood gas monitoring was used to maintain pH >7.35 and Po\(_2\) >100 mm Hg. Prophylactic bretylium (1 mg/min IV) was used to reduce the frequency of ventricular arrhythmias.

**Surgical Procedure**

The femoral vessels were isolated, and the veins were cannulated for drug administration. An 8F vascular sheath was introduced (USCI, Division of CR Bard, Billerica, Mass) into the right femoral artery for blood pressure monitoring and coronary catheterization. In group 3 animals, an 11F vascular sheath was placed in the left femoral artery for intra-aortic balloon pump counterpulsation. ECG limb leads were placed on group 3 dogs for IABP triggering.

A left thoracotomy was performed in the fifth interspace. The pericardium was opened and suspended in a cradle, and a 3.0-cm segment of the left anterior descending artery (LAD) was dissected free, usually distal to the first diagonal branch. The proximal 1.0 cm of dissected artery was delineated by two Silastic vessel snares. Immediately distal to the second vessel snare, a specially designed vascular occluder was placed that permitted easy manipulation of artery occlusion. Last, approximately 0.5 cm distal to the vascular occluder, a Doppler flow probe was placed (Triton Technology, San Diego, Calif) to measure continuous LAD flow velocity. Arterial blood pressure, ECG, phasic flow velocity, mean flow velocity, and ascending aortic blood pressure (for group 3 dogs) were continuously monitored. The instrumentation is shown in Fig 1. All septal perforating and branch arteries were suture-ligated between the Silastic snares.

A "critical" stenosis was then created using the vascular occluder, whereby peak flow velocity remained unchanged (±10\%) in the hyperemic period after 20 seconds of complete coronary occlusion by the proximal vessel snare. Once this degree of stenosis was achieved, the vascular occluder was no longer manipulated. Baseline measurements of LAD flow velocity, ECG, and blood pressure were obtained. Coronary arteriography was then performed via the standard Judkins technique using 5 to 8 mL of meglumine diatrizoate (MD-76, Mallinkrodt Medical, St Louis, Mo) and recorded on videotape to document vessel patency and the site of arterial stenosis.

**Thrombus Formation**

A guiding catheter was positioned in the ostium of the left coronary artery. An infusion catheter (Tracker-18 Hi-Flow, Target Therapeutics, San Jose, Calif) was advanced through the guiding catheter into the LAD. The distal end of the infusion catheter was positioned between the proximal and distal Silastic snares under fluoroscopic guidance. Careful visual inspection of the LAD showed that the catheter tip could be precisely located. Intimal injury was then created between the snares by four to five external compressions with a hemostat over 15 minutes. The snares then occluded the LAD, with complete cessation of coronary flow. Thrombin (0.3 mL, 100 U/mL; Armour Pharmaceutical, Kankakee, Ill) was mixed with 0.9 mL of blood and injected through the infusion catheter into the isolated segment. Confirmation of correct catheter placement was made by observing the vessel to "plump up" during infusion. The guide and infusion catheters were then carefully removed. Thirty minutes later, the proximal Silastic snare was removed, immediately followed by the distal snare. When coronary flow was observed to be absent for 15 minutes after distal snare release, complete thrombosis was believed to be established. This time was designated as 0 minutes.
In group 1, coronary angiography was performed at 0, 30, 60, 120, and 150 minutes to document the site of thrombosis and continued occlusion. In groups 2 and 3 dogs, the coronary artery was not imaged by angiography until the end of the experiment (t=150 minutes).

Once thrombosis was established in group 3, an intra-aortic counterpulsation balloon (40 mL, Dataspere, Montvale, NJ) was inserted through the 11F left femoral arterial sheath. Under fluoroscopic guidance, the tip of the balloon was placed distal to the aortic knob in the descending aorta.

Thrombolytic Therapy

Group 1 dogs served as controls and received no thrombolytic therapy. At time 0 minutes, groups 2 and 3 received a front-loaded regimen of rTPA (1.25 mg/kg, 15% as bolus, 50% over 30 minutes, and 35% over the next 60 minutes; Genentech, South San Francisco, Calif). IABP was begun at the initiation of rTPA therapy in group 3 and continued for 150 minutes. Balloon inflation began at the onset of diastole as determined by the dicrotic notch on the aortic pressure wave, and deflation occurred immediately before systole. LAD peak flow velocity, ECG, and arterial blood pressure were measured for 150 minutes after rTPA administration. Reperfusion was defined as return of LAD peak flow velocity to ≥60% of baseline. Reocclusion was defined as return of LAD flow to 0% of baseline peak flow velocity after reperfusion. Reocclusion time is the amount of time after initial reperfusion in which flow is absent because of cyclic arterial closure. Coronary arteriography was performed at the end of the experiment to document the degree of vessel patency or occlusion.

IABP and Coronary Flow Velocity

Five animals did not undergo coronary thrombosis (group 4) and had coronary blood flow velocity determined before and after IABP. The method of balloon catheter insertion was identical to group 3. Phasic blood flow velocity, mean velocity, aortic pressure, heart rate, and ECG were measured before and after the formation of critical stenosis. Critical stenosis was defined as in groups 1 through 3. Balloon inflation and deflation were performed as in group 3.

Statistical Analysis

All measurements are presented as a mean±SEM. At 0, 30, 60, 90, 120, and 150 minutes, each animal’s heart rate, systolic blood pressure, and diastolic blood pressure were adjusted by subtracting the respective baseline measurements. To test for significant changes in heart rate, systolic, and diastolic blood pressures between groups, a nonparametric one-way ANOVA was used (Statistical Analysis System NPAR1WAY procedure). This was performed at each of the time points. A Wilcoxon rank-sum statistic (correcting for continuity) was computed for these as well as for number of reocclusions, reperfusion time, time to initial reocclusion, and total flow duration measurements.

Results

Effect of IABP on Coronary Flow Velocity

In the absence or presence of LAD stenosis, IABP had no effect on mean LAD flow velocity as studied in group 4 dogs (98.0±3.7% of baseline, P=.55, and 96.6±1.8% of baseline, P=.13, respectively). As shown in a representative animal before stenosis formation (Fig 2), LAD peak flow velocity increases slightly immediately after turning the IABP on. However, by the sixth cardiac cycle, there is no difference compared with baseline. After the formation of a "critical" stenosis in the same animal, LAD peak flow velocity also transiently rises after IABP but then falls toward baseline (Fig 3).

Hemodynamic Observations in Animals Receiving Thrombolytic Therapy

Heart rate was similar throughout the experiment in groups 2 and 3. Systolic arterial pressure remained similar between these groups throughout the experiment (Fig 4). With IABP, peak diastolic blood pressure in group 3 animals remained significantly higher than the diastolic pressure in group 2 animals (Fig 5).

Reperfusion

Spontaneous reperfusion did not occur in any of the control animals in group 1. Reperfusion occurred in all animals treated with rTPA. Reperfusion occurred three times faster in those treated with IABP (13.1±2.1 minutes versus 39.2±9.4 minutes, P=.02).

Fig 2. Graph showing the effect of intra-aortic balloon counterpulsation (IABP) on peak coronary flow velocity in a representative group 4 animal without stenosis. IABP− indicates IABP absent; IABP+, IABP present.

Fig 3. Graph showing effect of intra-aortic balloon counterpulsation (IABP) on peak coronary flow velocity in the same animal in Fig 2 after critical stenosis has been created. IABP− indicates IABP absent; IABP+, IABP present.
Reocclusion and Total Flow Duration

Group 2 and group 3 animals experienced reocclusion at similar frequencies (2.2±0.4 versus 3.3±1.3 events, respectively, \( P = .85 \)). The time to initial reocclusion did not differ between group 2 (28.5±9.3 minutes) and group 3 (19.9±2.4 minutes, \( P = .40 \)). Because of reocclusion, total flow duration was not affected by IABP (94.9±15.3 versus 81.4±16.6 minutes, respectively, \( P = .52 \)).

Discussion

The most rapid and sustained restoration of infracted artery blood flow by intravenous thrombolytic therapy provides the greatest survival benefit in acute myocardial infarction.\(^2\) Extensive investigations to improve the time to reperfusion and prevent reocclusion have been performed. These studies have focused primarily on the hemostatic system, examining methods of platelet and coagulation pathway inhibition and their effects on reperfusion and reocclusion.\(^4\) However, the potential relation of arterial blood pressure to successful thrombolysis has not been well studied.

Basic physiological principles suggest several mechanisms whereby arterial blood pressure could affect reperfusion by thrombolytic therapy. First, arterial blood pressure, by being the inflow pressure, directly affects coronary blood flow in the presence of a severe coronary stenosis, and thus, the delivery of the thrombolytic agent to a partially occlusive thrombus. Also, by being the effective inflow pressure wave carrying the thrombolytic agent that impacts on the occlusive thrombus, the magnitude of the arterial pressure could be expected to exert a mechanically disruptive effect on the thrombus by creating defects in the thrombus. Finally, the pressure wave could possibly separate the obstructive thrombus from the vessel wall by vessel distension and facilitate the ingress of the thrombolytic agent. Both of these latter mechanisms could increase the surface area of the thrombus available for thrombolytic agent binding and potentially facilitate thrombolysis and reperfusion. Similar mechanisms have been proposed for the enhanced thrombolysis observed when thrombolytic agents are delivered pharmacomechanically in fluid jets by a local catheter in a canine model of pulmonary emboli.\(^12\)

In the present study, IABP was chosen as the method to create a second arterial pressure wave and to examine its effect on reperfusion and reocclusion after intravenous thrombolytic therapy. The peak diastolic augmented pressure achieved in our study was less than typically observed in humans, in part because of the greater compliance of the canine aorta.\(^13\) A model of coronary thrombosis similar to one previously described with incorporation of a stenosis was used.\(^10\) It has been shown that in the absence of this stenosis, reocclusion does not occur in this model. We included a control group (group 1) to exclude the potential confounding variable of spontaneous reperfusion.

The effects of IABP on coronary blood flow remain controversial. Kern et al\(^11\) did not observe an increase in coronary blood flow after intra-aortic balloon pumping in patients with severe coronary stenoses. In our model, we have found similar results. Mean coronary blood flow, in the presence of a stenosis that prevents an increase in peak flow velocity during reactive hyperemia, did not increase with intra-aortic balloon pumping. In addition to augmenting diastolic pressure, IABP decreases afterload. We cannot exclude an effect of decreased afterload on our findings, although it is not immediately apparent how this could affect reperfusion.

This study has shown that the augmentation of diastolic pressure by IABP, which in effect causes a second pressure wave during diastole, markedly enhances the velocity of reperfusion. The peak diastolic pressure in
The findings of this study may have particular relevance to the treatment of acute myocardial infarction associated with a depressed hemodynamic profile. In this subgroup of patients, intravenous thrombolytic therapy has not been beneficial. It has been postulated that the low patency rates achieved explain this lack of benefit. The demonstration that arterial pressure augmentation facilitates arterial opening, an event believed to be critical for survival in shock, may therefore have especially important implications for therapy in these patients.

Conclusions

Intra-aortic balloon counterpulsation enhances reperfusion by thrombolytic therapy in this canine model of coronary thrombosis. We hypothesize that this phenomenon is mediated by a primary mechanical effect of the augmented diastolic pressure wave and not by augmentation of coronary blood flow. This is the first study that demonstrates that arterial pressure augmentation facilitates the opening of thrombocytically occluded coronary arteries by thrombolytic therapy and suggests that reperfusion with rTPA may be blood pressure dependent. These findings have important implications for future myocardial infarction therapies, particularly in the setting of hypotension and shock. Further studies are needed to investigate the effect of pharmacological regulation of arterial blood pressure during thrombolysis.

Acknowledgments

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