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Adjunctive left ventricular unloading during myocardial reperfusion plays a major role in minimizing myocardial infarct size

Although prompt institution of reperfusion following coronary artery occlusion has been shown to limit myocardial infarct size, significant "reperfusion injury" may result. We investigated in a canine model whether maintenance of the left ventricle in an unloaded state during the initial reperfusion period following acute myocardial ischemia would result in greater limitation of infarct size or modify the development of reperfusion injury. Group I (control, n = 6) underwent 6 hours of occlusion of the left anterior descending coronary artery without further intervention. In both Group II (n = 6) and Group III (n = 6), the snare was released after 2 hours and hearts were reperfused for 4 hours. In Group III only, the left ventricle was maintained in an unloaded state throughout the entire reperfusion interval via pulsatile left atrial-femoral artery bypass. The results showed that reperfusion of the left ventricle in an unloaded state resulted in significantly improved limitation of both infarct size (area of infarct/area at risk = 16.6% for Group III versus 72.0% for Group I and 55.4% for Group II, $p < 0.001$) and area of microvascular damage (area of microvascular damage/area at risk = 4.8% for Group III versus 30.6% for Group II, $p < 0.001$). These results indicate that although myocardial reperfusion of the type provided by thrombolysis and/or angioplasty techniques does result in limitation of infarct size when compared to no reperfusion, this limitation is not optimal unless the left ventricle is unloaded during the initial reperfusion period..

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Reperfusion after acute myocardial ischemia has recently attracted much clinical interest. Present modalities of reperfusion include immediate bypass grafting and lysis of thrombi with fibinolytic agents.[1-8] Thrombolytic therapy offers advantages in that thrombolysis can be completed earlier in the course of the ischemic period than can bypass grafting and is less traumatic. However, thrombolysis may fail to occur or may be delayed, and the persistence of significant flow-reducing lesions can render reperfusion suboptimal.[9]

Many experimental studies have indicated that, in general, reperfusion following acute myocardial ischemia results in significant myocardial salvage.[9,10] Other studies, however, have suggested that "reperfusion injury" can result, which may limit or negate the effectiveness of reperfusion.[10-15] Furthermore, recent experimental evidence indicates that ischemic myocardium is more effectively salvaged by revascularization following ischemic arrest and hypothermic myocardial protection than by reperfusion of the heart in the beating, working state.[16] This previous study suggests that the degree of infarct limitation seen with simple reperfusion of the beating, working heart may be suboptimal and that simple reperfusion can actually result in infarct expansion and development of reperfusion injury due to the physiological conditions present at the time of reperfusion. As a result, we undertook this study of reperfusion following acute myocardial ischemia in dogs to determine if control over the conditions of reperfusion via temporary left heart bypass would help to limit infarct size. In addition, we sought to determine whether left

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ventricular (LV) unloading during reperfusion would suppress development of reperfusion injury.

Materials and methods

Experimental preparation. Eighteen dogs weighing 20 to 25 kg were anesthetized with intravenous morphine sulfate (2 mg/kg) and chloralose (100 mg/kg). After intubation, respiration was controlled with a positive-pressure ventilator supplying a mixture of room air and low flow oxygen. Following left-sided thoracotomy, the left anterior descending coronary artery (LAD) was identified, dissected 2 cm from its origin from the left main coronary artery and proximal to the first large diagonal, and snared with a 2-0 silk ligature. Catheters were placed in the left atrium (LA) and aortic root for continuous pressure monitoring and blood sampling. A catheter was also placed in the chamber of the left ventricle (LV) through the apex for continuous monitoring of generated intraventricular pressure and for instantaneous calculation of the tension-time index by an integrating circuit. Radioactive microspheres (^{125}I, ^{85}Sr, ^{141}Ce, ^{46}Se) were injected at intervals into the LA, and aortic root samples were obtained for determination of regional myocardial blood flow.[17]

Experimental protocol. The LAD was ligated for 2 hours in all animals. Measurements of systemic, LA, and LV pressures, tension-time index, and regional myocardial blood flow were obtained immediately prior to LAD ligation and monitored throughout the 2 hour ligation interval. At the end of this initial ligation interval, animals were randomly divided into three groups of six animals each. In the six control animals (Group I) no further interventions were carried out, and the LAD ligation interval was merely extended for an additional 4 hours. Thus, in these animals the total ischemic interval in the LAD distribution was 6 hours. Heart rate and blood pressure were monitored continuously throughout this 6 hour ischemic interval and maintained within 10% of baseline values by administration of fluids when necessary, appropriate adjustment of respirator settings, and pacing in instances of severe bradycardia. No pharmacologic agents other than sodium bicarbonate for treatment of metabolic acidosis were administered.

Six other animals were placed in Group II at the end of the initial 2 hour ligation interval. The Group II animals underwent 4 hours of reperfusion without any adjunctive support or therapy. Again, heart rate and blood pressure were monitored continuously throughout this 4 hour reperfusion interval and were maintained within 10% of baseline values by addition of intravenous fluids, appropriate adjustment of respirator settings, and pacing in instances of bradycardia. No pharmacologic agents other than sodium bicarbonate were administered. The remaining six animals (Group III) also underwent 4 hours of reperfusion. In contrast to Group II, however, Group III animals were placed on a pulsatile left atrial–femoral artery (PLA-FA) bypass system immediately prior to the start of the reperfusion period.

A 32 Fr. cannula was placed in the LA and used to remove all blood entering this chamber so that complete unloading of the LV was accomplished. After passing through the pulsatile pump circuit, blood was returned to the animal via an 18 Fr. catheter placed in the right femoral artery. The PLA-FA bypass was initiated at a flow rate of approximately 1 L/min and was gradually increased until complete LV decompression was achieved. Body temperature was maintained at 37° C by means of a heat exchanger in the bypass circuit. Full heparinization (3 mg/kg/hr) was maintained throughout the entire reperfusion interval, but no other pharmacologic agents were administered. A mean aortic perfusion pressure of 85 to 100 mm Hg was maintained during the 4 hour reperfusion interval by adjustment of pump flow rate and addition of intravenous fluids. The extracorporeal PLA-FA bypass system used in this group of animals provided pulsatile one-way flow by means of a hydraulically driven bladder pump system. Inflow and outflow valves were placed on either side of the pumping chamber to ensure delivery of one-way pulsatile flow from the LA to the FA. The hydraulic drive system was synchronized electronically to the electrocardiogram so that pulsatile flow was delivered during electrical diastole. The pump generated a mean pulse pressure of 45.2 ± 6.3 mm Hg throughout the bypass period. The relative advantages of this pulsatile LA-FA bypass system compared to a similar but nonpulsatile LA-FA bypass system have been described previously.[18]

In all Group II (reperfusion alone) and Group III (reperfusion plus PLA-FA) animals, Monastral blue B (3%, 2 ml/kg), a macromolecular pigment used to detect increased microvascular permeability or stasis, was infused intravenously during a 15 minute period immediately prior to release of the LAD snare and reperfusion of the previously ischemic areas of myocardium. The use of Monastral blue in this fashion allowed later gross delineation of areas of microvascular damage resulting in leakage or stasis and plugging, which had occurred at any time from the onset of reperfusion.[19]

At the end of reperfusion in all groups, a 1% solution of gentian violet (3 ml/kg) was injected into the LA for 30 seconds, during which the hearts were allowed to beat

Table I. *Comparison of various parameters*

	Group I: Control	*Group II: Reperfusion*	*Group III: Reperfusion + PLA-FA bypass*
AR (% of LV)	27.2 ± 2.5	32.2 ± 1.4	28.1 ± 2.3
Endo/epi (% change)	−19.8 ± 8.6	−20.2 ± 12.9	+29.8 ± 27.0†
TTI (% change)	0 ± 3	0 ± 12	−87.5 ± 6‡
AI/AR (%)	72.0 ± 4.4	55.4 ± 7.7*	16.6 ± 8.5‡
AMD/AR (%)	–	30.6 ± 3.0	4.8 ± 2.9§

Legend: Comparison of various parameters among groups that underwent 6 hours of ischemia alone (Group I), 2 hours of ischemia followed by 4 hours of reperfusion (Group II), or 2 hours of ischemia followed by 4 hours of reperfusion with the left ventricle unloaded (Group III). Values are the mean ± the standard error of the mean for each group. AI, Area of infarct. AMD, Area of microvascular damage. AR, Area at risk of infarction. Endo/epi, Endocardial/epicardial flow ratio. LV, Left ventricle. PLA-FA, Pulsatile left atrial–femoral artery. TTI, Tension-time index.

*$p < 0.05$ versus Group I.

†$p < 0.05$ versus Groups I and II.

‡$p < 0.001$ versus Groups I and II.

§$p < 0.001$ versus Group II.

in a fully ejecting state to allow distribution of the pigment throughout the coronary circulation. Before gentian violet injection in Groups II and III was begun, the previously released snare around the LAD was religated. After distribution of the dye, hearts were electrically fibrillated and rapidly excised so as to prevent washout of the gentian violet solution. The LV and septum were separated from the remainder of the heart and sliced transversly into nine sections 3 to 4 mm thick. These slices were placed between two transparent plastic sheets for planimetry of the area unstained by gentian violet, i.e., the area at risk for infarction, and the total area of the LV.[18, 20-24] The slices were then immersed for 20 minutes in a 37° C bath of triphenyltetrazolium chloride dye. Areas of myocardium not grossly discolored after this incubation were considered areas of infarct and were also measured by planimetry.[21, 24] Finally, areas of microvascular damage stained with Monastral blue were identified and measured by planimetry.

Unless otherwise noted, all values are reported as the mean ± standard error of the mean for each group of animals. The statistical significance of differences was determined by analysis of variance.

Results

The results of these experiments are summarized in Table I. The area at risk for infarction, measured as a percentage of the LV, did not differ significantly between groups and ranged from 27% to 32%. Thus, large areas of the LV in each group were placed at risk for infarction.

Significant decreases from baseline in regional myocardial blood flow (endocardial/epicardial flow ratio) as determined by radioactive microsphere distribution occurred in control animals after 3 hours of LAD ligation (Group I = −19.8 ± 8.6%, $p < 0.05$ versus baseline), as well as in those animals that underwent reperfusion alone after 2 hours of LAD ligation plus 1 hour of reperfusion (Group II = −20.2 ± 12.9%, $p < 0.05$ versus baseline). In contrast, animals supported with PLA-FA during reperfusion (Group III) showed an increase from baseline in the endocardial/epicardial flow ratio (+29.8 ± 27.0%) after 2 hours of LAD ligation plus 1 hour of supported reperfusion. When compared with the results in Group I and Group II animals, these differences in Group III endocardial/epicardial flow changes were significant at the $p < 0.05$ level.

The tension-time index remained unchanged from baseline in Group I (0 ± 3%) and Group II (0 ± 12%) animals over the 6 hour protocol. However, institution of PLA-FA bypass in Group III animals resulted in a significant decrease in tension-time index from baseline over the 6 hour period (−87.5 ± 6%). When compared with the indices in both Group I and Group II animals, the change in tension-time index in Group III was highly significant ($p < 0.001$).

Group I control animals sustained large LV infarcts, and when the size of the infarct was expressed as a percentage of the area at risk (area of infarct/area at risk), almost 75% of the area at risk (72.0 ± 4.4%) was found to have progressed to complete infarction. In Group II animals undergoing reperfusion alone, a significant limitation of infarct progression was noted (area of infarct/area at risk = 55.4 ± 7.7%, $p < 0.05$ versus Group I). However, the Group III animals that underwent reperfusion with adjunctive PLA-FA bypass showed the most significant limitation of infarct size (area of infarct/area at risk = 16.6 ± 8.5%, $p < 0.001$ versus Group I and Group II).

Finally, in those animals undergoing reperfusion

alone (Group II), significant microvascular damage was noted. In such animals, the area of microvascular damage/area at risk for infarction averaged 30.6% ± 3.0%. In contrast, in those animals undergoing reperfusion during adjunctive PLA-FA bypass (Group III), only 4.8% ± 2.9% of the area at risk went on to develop microvascular damage as indicated by Monastral blue staining ($p < 0.001$ versus Group II).

Discussion

Previous investigations have revealed that the institution of reperfusion in the beating, working heart after as long as 6 hours of ischemia results in limitation of infarct size.[9, 10] Some investigators, however, have noted striking, deleterious histologic changes in hearts undergoing such reperfusion. Simple reperfusion of ischemic myocardium has been shown to accelerate the disintegration of irreversibly injured myocytes, resulting in disruption of the sarcolemma, loss of volume regulation, contraction band necrosis, and calcium loading of the mitochondria.[9, 10, 25-30]

Such morphologic changes have been associated with an accelerated washout of creatine kinase in the initial phase of reperfusion.[9] In addition, significant reperfusion injury as evidenced by microvascular damage within the zone of necrosis has been demonstrated by most investigators and has been found to be associated with hemorrhage into areas of the injured tissues.[9, 10, 31-36] Finally, numerous investigators have described a "no reflow" phenomenon in which microvascular damage or other factors actually prevent reperfusion of ischemic myocardial regions.[9, 37, 38] Suggested causes of this no reflow phenomenon include endothelial damage, myocyte swelling, development of contraction bands, and plugging of the capillaries by granulocytes or erythrocytes.[39]

Since reperfusion does decrease the ultimate overall size of the myocardial infarct, it has been commonly thought that reperfusion injury merely hastened the evolution of changes leading to cell death in a given population of cells considered to have been irreversibly injured.[9, 10] Therefore, it has been suggested that such results should not represent a deterrent to simple reperfusion for salvage of the reversibly injured myocytes. As a result, investigators have postulated that simple reperfusion alone results in maximal limitation of evolving infarct size and that the microvascular damage, hemorrhage, and histologic changes associated with reperfusion are not significantly detrimental, since such injuries are limited to areas already affected by irreversible myocyte damage.

In contrast, the present study investigated the hypothesis that further infarct expansion may occur upon reperfusion. This study also examined the hypothesis that control of the conditions of reperfusion may have a significant effect not only on limiting this infarct expansion associated with reperfusion of an acute infarct, but also on limiting the subsequent development of reperfusion injury. The results demonstrate that although myocardial reperfusion of the type provided by thrombolytic and/or angioplastic techniques does result in significant limitation of infarct size when compared to no reperfusion, this limitation is not optimal because a significant amount of reperfusion injury results and further limitation of infarct size is possible. On the other hand, maintenance of the LV in a beating but *non*-working state via PLA-FA bypass during the reperfusion interval not only results in the minimization of infarct size, but also significantly reduces the extent of microvascular reperfusion injury as detected by Monastral blue staining. These results suggest that adjunctive use of PLA-FA bypass to keep the LV in an unloaded state during reperfusion, as opposed to simple reperfusion alone, not only reduces further infarct expansion following reperfusion, but also prevents the microvascular damage that has been shown to occur in conjunction with simple reperfusion of the beating, working heart.

Several factors can be postulated as being partially responsible for the dramatic decreases in infarct size and reperfusion injury observed with reperfusion under conditions of PLA-FA bypass (Group III). First, in animals undergoing reperfusion with adjunctive PLA-FA bypass, the endocardial/epicardial flow ratio was significantly increased when compared to those of both control and reperfusion-alone animals. Thus, in Group III animals the deleterious early redistribution of myocardial blood flow seen in animals without PLA-FA support was avoided. In addition, the tension-time index in those animals undergoing reperfusion in conjunction with PLA-FA bypass was decreased 85.5% when compared to baseline ($p < 0.001$ versus Groups I and II). In contrast, in control and reperfusion-alone animals, tension-time index remained essentially unchanged when compared to baseline.

Therefore, the addition of PLA-FA bypass to reperfusion resulted in significant decreases in myocardial work while simultaneously preventing early redistribution of myocardial blood flow away from the especially vulnerable subendocardial layer. These favorable events resulted in the greatest degree of infarct limitation of the three groups as well as prevention of reperfusion injury as detected by microvascular damage.

In summary, these data demonstrate that adjunctive use of PLA-FA bypass during the early reperfusion

period after acute myocardial ischemia in dogs significantly improves myocardial salvage and reduces microvascular damage when compared to simple reperfusion alone. Such striking improvements through the use of PLA-FA bypass are probably due to the decreased myocardial oxygen demands evidenced by the reduction of tension-time index as well as to prevention of the redistribution of myocardial blood flow away from subendocardial layers. This demonstration of the ability of PLA-FA bypass to significantly improve myocardial salvage and reduce microvascular damage upon reperfusion emphasizes the vulnerability of ischemic myocardium to further injury during the reperfusion period. These data suggest that simple reperfusion of the type provided by thrombolytic and/or angioplasty techniques may actually promote infarct expansion and development of reperfusion injury.

Percutaneous implementation of PLA-FA bypass may prove to be a highly useful adjunct to further nonsurgical and surgical attempts to promptly revascularize acutely ischemic myocardium. The ability to control the conditions of reperfusion which the use of PLA-FA bypass confers results in minimization of infarct size along with prevention of reperfusion injury and thus should allow more complete functional recovery of the myocardium. Experiments are now underway to determine whether the observed immediate advantages resulting from use of PLA-FA bypass during early reperfusion are permanent benefits or whether the infarct resumes expansion when the injured and reperfused heart is weaned from PLA-FA bypass.

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