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Basic Science Review

Left Ventricular Unloading With Intra-aortic Counter Pulsation Prior to Reperfusion Reduces Myocardial Release of Endothelin-1 and Decreases Infarction Size in a Porcine Ischemia-Reperfusion Model

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Objectives: We tested the hypothesis that unloading the left ventricle with intra-aortic balloon counter-pulsation just prior to reperfusion provides infarct salvage compared with left ventricular (LV) unloading postreperfusion or reperfusion alone. Background: Previous reports demonstrated infarct salvage with complete LV unloading with an LVAD prior to reperfusion; however, partial LV unloading using intra-aortic balloon pumps (IABPs) has not been evaluated. Methods: Twenty-eight Yorkshire pigs were subjected to 1 hr of left anterior descending artery occlusion and 4 hr of reperfusion. An IABP was inserted and activated just prior to reperfusion (IABP-Pre), or 15 min after reperfusion (IABP-Post), or not at all (control). Results: At baseline, the hemodynamic data were similar in the three groups. Myocardial infarct size expressed a percentage of zone at risk in control animals was 44.9% ± 4.8%, IAPB-Pre group 20.9% ± 5.1% ($P < 0.05$ compared to control), and IABP-Post group 33.2 ± 6.1% ($P = 0.16$ vs. control group). There was a correlation between transcardiac endothelin-1 release at 15 min postreperfusion and infarct size ($r = 0.59$). Conclusion: LV unloading with an IABP prior to reperfusion reduces the extent of myocardial necrosis in hearts subjected to 1 hr of left anterior descending artery occlusion and 4 hr of reperfusion compared with either reperfusion alone or LV unloading after reperfusion. Inhibition of myocardial ET-1 release by LV unloading may be a significant mechanism of myocardial protection. These data suggest that in high-risk STEMI patients, IABP unloading prior to reperfusion might be more beneficial than IABP placement postreperfusion. © 2008 Wiley-Liss, Inc.

Key words: coronary flow (CFLO); intra-aortic balloon pump (IABP); acute coronary syndrome (ACS); cardiopulmonary support (CPS); percutaneous coronary intervention (PCI)

INTRODUCTION

The benefit and the optimal timing of initiation of intra-aortic balloon pump (IABP) counter-pulsation use in high-risk patients with acute myocardial infarction treated with primary angioplasty has not been well documented. Several studies which used IABP following primary PTCA in high-risk patients in an attempt to improve outcomes yielded conflicting results [1–6]. As shown in Table I, IABP placement prior to revascularization in high-risk STEMI patients provided benefit as opposed to placement of the IABP after revascularization which showed little benefit if any. Previous studies reported that left ventricular (LV) unloading in acute myocardial infarction may limit

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TABLE I. Previous IABP Trials in High-Risk STEMI Patients

Study	*n*	Setting	Groups	Endpoints	% Endpoints (*P* value)
Brodie et al. [5]	238	High-risk primary PCI	IABP prior to intervention ($n = 78$) vs. IABP post intervention or not at all ($n = 160$)	Ventricular fibrillation	10.3 vs. 14.4 (0.38)
				Cardiopulmonary arrest	5.1 vs. 13.1 (0.06)
				Hypotension	0 vs. 6.9 (0.02)
				Any event	11.5 vs. 21.9 (0.05)
Stone et al. [6]	437	High-risk primary PCI	IABP after intervention ($n = 221$) vs. traditional care ($n = 226$)	Death	4.3 vs. 3.1 (0.52)
				Reinfarction	6.2 vs. 8.0 (0.46)
				Infart-related artery occlusion	6.7 vs. 5.5 (0.64)
				Congestive failure/hypotension	19.9 vs. 23 (0.43)
				Primary endpoint	28.9 vs. 29.2 (0.95)

reperfusion injury and infarct size possibly by improving coronary blood flow and reducing the workload of the heart [7–11]. The majority of previous mechanistic experiments in animal models used LV assist devices which are not readily available for clinical use. The IABP, on the other hand, is widely available and easy to insert but has somewhat limited unloading capacity. Therefore, some skepticism exists regarding its ability to provide enough ventricular unloading to produce a clinically meaningful effect other than to support the blood pressure and reduce after-load.

Ventricular unloading has been shown to reduce the incremental damage of the myocardium induced by ischemic-reperfusion injury [7–11]. Given the available information to date, it appears that following a large myocardial infarct, LV wall stress is increased and triggers deleterious adaptation processes, including production of intracardiac angiotensin II, cardiac endothelin formation and release, and proapoptotic signaling for cardiomyocytes [12]. ET-1 is a potent activator of the sodium/hydrogen exchanger. There is convincing evidence that the sodium/hydrogen exchanger plays a pivotal role in mediating tissue injury during ischemia and reperfusion [13–16]. It has been shown that the sodium/hydrogen exchanger is activated on reperfusion, and that its inhibition delays re-alkalization and decreases intracellular Na^+, and via Na^+/Ca^{2+} exchange, Ca^{2+} overload [17]. Attenuated Ca^{2+} overload and prolonged acidosis are known to be cardioprotective [18,19]. The purpose of this study was to test the hypothesis that LV unloading with the IABP in an acute porcine myocardial infarction model, prior to but not after reperfusion results in infarct salvage similar in magnitude and by similar mechanisms observed with LV assist devices.

METHODS

Studies were carried out in 28 Yorkshire pigs of either sex weighing 48 ± 2 kg. The study protocol was approved by the Animal Welfare Committee of the University of Texas at Houston Medical School and all experiments were performed according to the Committee's guidelines.

Surgical Preparation

Animals were sedated with Telazol (4.0 mg/kg, IM) and Robinul (0.0009 mg/kg, IM), and intubated. General anesthesia was initiated with 5% isoflurane gas induction, and then reduced to 2–3% maintenance. A median sternotomy was performed. Rectal temperature was kept at 38–39°C by means of a heating pad.

The pericardium was opened and the heart was suspended in a pericardial cradle. A ligature was placed around the left anterior descending (LAD) artery at a position from which the distal third of the artery would be occluded by tightening the ligature. A catheter was placed in the LV cavity through the apex of the heart for measurement of LV pressure. Catheters were placed in the left atrial appendage for injection of radioactive microspheres and for monitoring left atrial pressure, and an additional catheter was placed in the internal carotid and advanced to the ascending aorta for measurement of aortic pressure, for aortic blood sampling during microsphere injection, and for aortic ET-1 sampling. A catheter was inserted in the left external jugular vein and advanced into the coronary sinus (CS) under fluoroscopic guidance for ET-1 blood sampling withdrawal. The 35-mL Datascope intra-aortic balloon catheter was placed via cut-down into the left femoral artery and advanced under fluoroscopic control to the descending aorta. Sham operated animals received the pump, but counter-pulsation was not initiated.

In addition, amiodarone was administered for arrhythmia suppression with a loading dose of 5.0 mg/kg prior to the sternotomy and bolus infusions of 3–5 mg/kg were administered prior to occlusion and reperfusion, and when needed, throughout the procedure. Intravenous lidocaine (1–2 mg/kg) was administered in bolus infusions and a drip started and maintained throughout the occlusion period and for 4 hr of reperfusion. Low-dose phenylephrine (20 mcg/min) was administered to maintain mean arterial pressure at 70–90 mm Hg in 16 of the animals.

All animals received acetylsalicylic acid IV (300 mg) the day prior to and clopidogrel (75 mg) for 2 days prior to the experiment. Sodium heparin (150 U/kg bolus) followed by an IV drip was used to maintain an activated clotting time of greater than 200 sec until the end of the experiment.

Experimental Protocol

After instrumentation and stabilization, baseline measurements including hemodynamic values (aortic pressure, left atrial and LV pressures, heart rate) were recorded. Blood samples for regional myocardial blood flow (RMBF), using radioactive microspheres, and arterial and CS endothelin-1 levels were taken. After baseline measurements were obtained, the LAD artery was occluded for 1 hr. Reperfusion was allowed for 4 hr. Hemodynamic values and flow data were continuously recorded. Blood samples for plasma ET-1 content were collected simultaneously from the CS and the descending thoracic aorta at baseline and at 30 and 45 min of ischemia and at the time of reperfusion, 15 min, 30 min, 1 hr, 2 hr, 3 hr, and 4 hr of reperfusion.

Animals were randomized to three groups. Group 1 served as a group control, and no support was given (sham IAPB insertion). In group 2 (IABP-Pre), the IABP was started 15 min prior to reperfusion and maintained the entire reperfusion period. In group 3 (IABP-Post), IABP was initiated 15 min after reperfusion and maintained for the rest of the reperfusion period. Of the 28 animals, 10 suffered refractory ventricular fibrillation and did not complete the study and were excluded from the analysis, leaving six animals in each group.

Infarct Size Quantification

After the 4-hr reperfusion period was completed, additional intravenous sedation with sodium pentobarbital was administered, and the animals were sacrificed with an injection of supersaturated potassium chloride. The hearts were quickly excised and rinsed with tap water. A perfusion cannula was inserted into the LAD artery at the level of the snare and the ascending aorta was attached to a perfusion stand. Simultaneously, the LAD artery was perfused with a 1% solution of triphenyltetrazolium chloride buffered to pH 7.5, and the aortic root was perfused with 1% Evans blue at equal pressure (100 mm Hg) for 3 min to delineate the risk and control regions. After perfusion, the atria and right ventricle was excised and the left ventricle was sliced in ''bread loaf'' fashion from base to apex into six to seven 1-cm-thick sections. Each slice was then weighed. The tissue slices were then incubated in triphenyltetrazolium chloride at 37°C for an additional 30 min to ensure proper staining of ischemic but viable tissue. The triphenyltetrazolium chloride stained the risk region containing residual viable tissue as brick red, while the infarcted tissue remained unstained and appeared tan [20]. The nonischemic region (control region) was stained by the Evans blue. After triphenyltetrazolium chloride staining, both surface of each ventricular slice were traced on acetate film to show the histochemical demarcation of the infarct, risk, and control regions. Their respective areas were planimetered and multiplied by the slice weight to determine infarct size as a percentage of myocardium at risk and total ventricular mass.

Tissue samples were obtained from the ischemic zone at risk (ZR), the infarct zone, the border epicardial region in the circumflex and septal borders, and in the nonischemic or control region (stained blue). The slices were fixed in formalin and samples were taken from representative endocardial, mid-wall, and epicardial areas for calculation of microspheres RMBF measurements.

Regional Myocardial Blood Flow

At baseline, 40 min occlusion, and 5 min reperfusion, 3 to 5 million 15-μm radioactive microspheres (NEN-TRAN, DuPont) were injected in a volume of 1 mL through the left atrial catheter over 30 sec, followed by 15 mL of normal saline. During the microsphere injection, arterial blood was continuously withdrawn from the ascending aorta for a period of 3 min with the use of a Harvard pump at a flow rate of 7 mL/min. Cerium 141, Tin 113, Sr 85, Nb 95, and Sc 46 gamma emitters were used at different time points for RMBF determination. Samples representative from the endocardial, mid-wall, and epicardial areas were taken from LV slices fixed in formalin for calculation of microsphere RMBF measurements using a LKB gamma counter (1282 Compugamma, LKB-Wallace, Turku, Finland). The energy windows were adjusted for the peak emission of the isotopes used for calculation of RMBF according to the method of Heymann et al. [20]. Segments in the histochemically defined ischemic regions were chosen for comparison of RMBF, and those with a transmural RMBF during coronary occlusion greater than 0.2 mL/min/g of myocardium were excluded due to the presence of collateral flow. Mean transmural blood flow less than 0.2 mL/min/g has been shown to correlate with severe functional impairment (akinesis or dyskinesis) of the involved myocardium and corresponds to the level of flow at which myocardial necrosis is first evident.

Plasma Endothelin-1 Content

Plasma ET-1 concentration was determined using commercially available radioimmunoassay kit (Peninsula Laboratories, San Carlos, CA) specific for ET-1.

TABLE II. Hemodynamic Parameters

		Occlusion			Reperfusion						
	Baseline	10 min Pump Off	30 min Pump Off	55 min Pump Off/On	10 min Pump Off/On	30 min Pump On	1 hr Pump On	2 hr Pump On	3 hr Pump On	4 hr Pump On	4 hr Pump Off
HR (beats per minute)											
Control	74 ± 3	72 ± 4	69 ± 2	68 ± 2	68 ± 3	68 ± 2	68 ± 2	69 ± 2	72 ± 4	70 ± 3	71 ± 3
IABP Pre	74 ± 5	63 ± 3	63 ± 3	61 ± 4	62 ± 4	63 ± 3	65 ± 3	72 ± 4	75 ± 4	78 ± 4	78 ± 5
IABP Post	76 ± 4	64 ± 3	64 ± 3	64 ± 2	62 ± 3	65 ± 3	67 ± 3	69 ± 4	73 ± 5	71 ± 4	74 ± 4
MAP (mm Hg)											
Control	72 ± 7	61 ± 8	63 ± 7	61 ± 6	62 ± 7	66 ± 7	68 ± 7	68 ± 9	66 ± 9	65 ± 9	64 ± 9
IABP Pre	86 ± 4	69 ± 3	74 ± 3	72 ± 4	70 ± 7	75 ± 6	72 ± 5	75 ± 7	68 ± 7	65 ± 6	62 ± 10
IABP Post	82 ± 4	64 ± 5	70 ± 4	74 ± 10	60 ± 9	73 ± 7	71 ± 5	70 ± 5	69 ± 4	65 ± 4	62 ± 5
LVSP (mm Hg)											
Control	89 ± 6	75 ± 6	78 ± 7	76 ± 5	78 ± 7	83 ± 6	85 ± 6	85 ± 9	83 ± 10	81 ± 10	80 ± 10
IABP Pre	103 ± 4	84 ± 4	90 ± 3	80 ± 4	81 ± 7	80 ± 6	78 ± 6	80 ± 8	78 ± 5	73 ± 7	80 ± 10
IABP Post	98 ± 4	77 ± 4	85 ± 4	90 ± 12	75 ± 8	78 ± 7	76 ± 6	74 ± 5	73 ± 4	70 ± 3	80 ± 3
LVEDP (mm Hg)											
Control	12 ± 1	14 ± 1	16 ± 1	17 ± 1	17 ± 2	17 ± 1	17 ± 1	15 ± 2	12 ± 1	12 ± 1	12 ± 1
IABP Pre	12 ± 2	17 ± 2	17 ± 2	17 ± 3	16 ± 3	16 ± 3	16 ± 4	13 ± 3	10 ± 2	9 ± 2	10 ± 3
IABP Post	13 ± 3	18 ± 2	21 ± 2	20 ± 2	19 ± 2	15 ± 2	15 ± 2	14 ± 2	12 ± 2	11 ± 2	12 ± 2
Mean LAP (mm Hg)											
Control	6 ± 1	8 ± 1	8 ± 1	9 ± 0	10 ± 1	10 ± 1	10 ± 1	9 ± 1	8 ± 1	8 ± 0	7 ± 0
IABP Pre	6 ± 2	9 ± 1*	9 ± 1*	9 ± 2	9 ± 2	9 ± 2	7 ± 2	5 ± 1†	6 ± 2	5 ± 2	6 ± 2
IABP Post	9 ± 1	12 ± 1	13 ± 2‡	11 ± 2	11 ± 2	10 ± 2	9 ± 2	9 ± 1	7 ± 1	8 ± 2	9 ± 1
RPP											
Control	65 ± 3	53 ± 5	53 ± 5	51 ± 4	52 ± 5	57 ± 4	56 ± 4	59 ± 7	60 ± 8	56 ± 7	56 ± 7
IABP Pre	76 ± 6	54 ± 5	57 ± 3	49 ± 4	51 ± 6	50 ± 5	60 ± 6	57 ± 8	57 ± 8	57 ± 7	65 ± 11
IABP Post	75 ± 5	50 ± 4	55 ± 4	58 ± 9	47 ± 6	51 ± 6	52 ± 5	52 ± 5	54 ± 6	50 ± 4	59 ± 4
Augmented diastolic aortic pressure (mm Hg)											
Control	–	–	–	–	–	–	–	–	–	–	–
IABP Pre	–	–	–	91 ± 5	94 ± 8	95 ± 6	90 ± 7	93 ± 7	86 ± 7	83 ± 6	–
IABP Post	–	–	–	–	–	91 ± 8	83 ± 10	87 ± 6	85 ± 4	80 ± 4	–

Values are expressed as means ± SEM. IABP, intraaortic balloon pump; HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure; LAP, left atrial pressure; RPP, rate pressure product.
*$P < 0.05$ IABP Pre vs. IABP Post; †$P < 0.05$ IABP Pre vs. Control; ‡$P < 0.05$ IABP Post vs. Control.

All the samples were performed in duplicate. The blood samples (7–8 mL) were collected into a chilled syringe and transferred into polypropylene tubes containing ethylenediaminetetraacetic acid (1 mg/mL of blood) and aprotinin (500 KIU/mL of blood). Plasma was separated by centrifugation at 1,500 rpm for 15 min at 4°C. The serum was transferred into new polypropylene tubes and stored at −80°C for up to 1 month. The extraction was performed using a Sep-column containing C_{18} (Peninsula Laboratories, San Carlos, CA). For the RIA, samples and standards were incubated with rabbit anti-ET serum for 24 hr at 4°C. Second 24-hr incubation was made after adding an iodinated tracer [^{125}I]-ET-1. Free and bound radioligands were separated with centrifugation and radioactivity in the precipitate was counted using a LKB gamma counter (1282 Compugamma, LKB-Wallace).

Statistical Analysis

Continuous data are presented as mean ± SEM. Direct comparison between groups were analyzed with Student's t test or analysis of variance (ANOVA) followed by Newman–Keuls test for post-hoc testing (Statistica, Tulsa, Oklahoma). ANCOVA was performed to compare the infarct size with the IABP-Pre and IABP-Post, as well as the controls, with plasma ET-1 as a covariate. Significant differences between groups were defined as $P < 0.05$.

RESULTS

Effects of LV Unloading on Hemodynamics

Hemodynamic changes during the baseline state, occlusion, and reperfusion are shown in Table II. At baseline or during coronary occlusion and reperfusion, there was no significant difference in mean heart rate, aortic pressure, or rate-pressure product among the groups. The effect of counter-pulsation on the LV developed systolic pressure as shown in Fig. 1a. There was a marked drop at the time of reperfusion (box A) in the pre-IABP group. Both IABP groups maintained significant reductions during reperfusion (box B). In addition, there was a significant drop in the end diastolic aortic

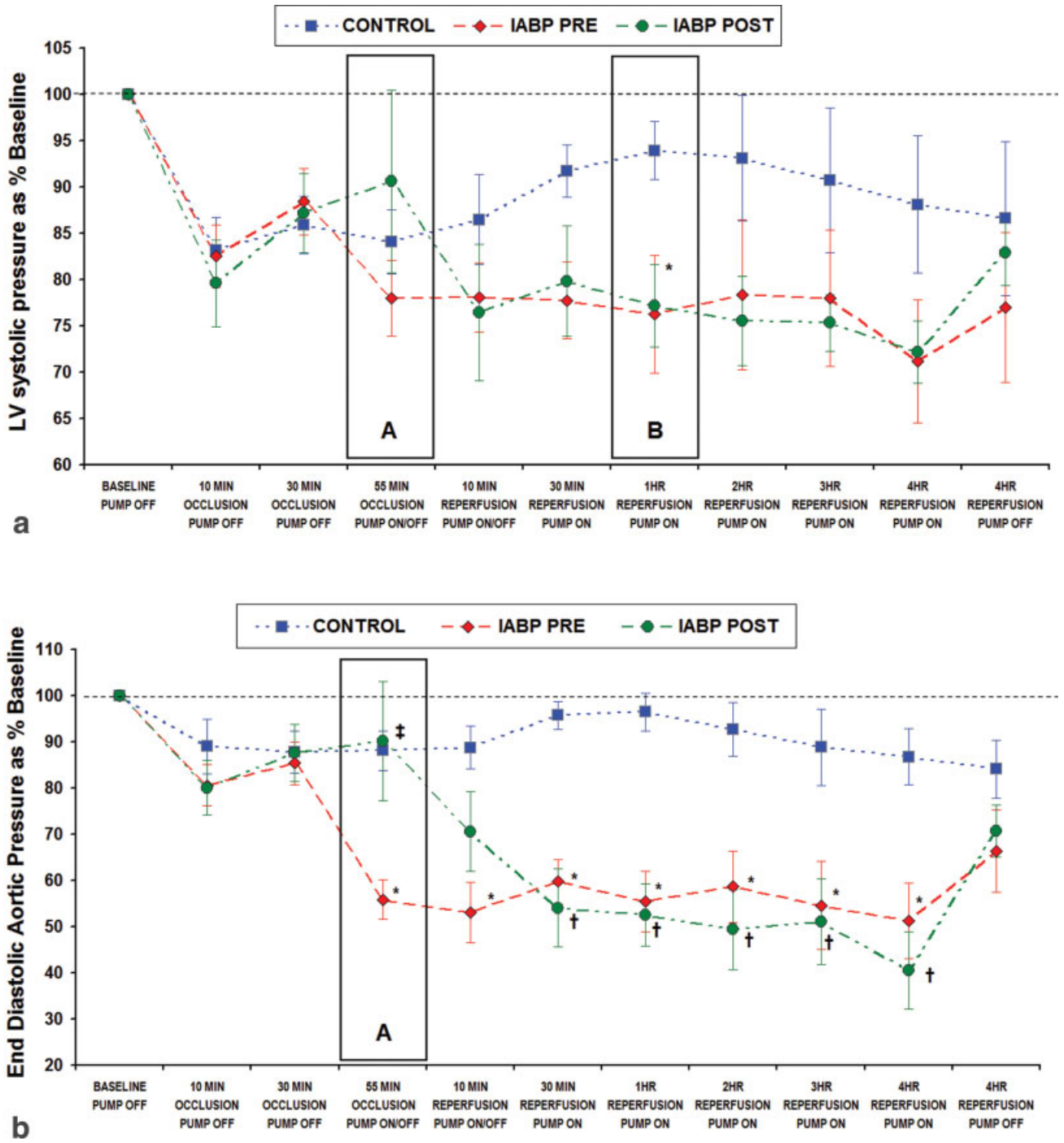

Fig. 1. (a) Relative change in the LV systolic pressure in the IABP-Pre, IABP-Post, and control groups. LV systolic pressure compared between the three groups over the course of reperfusion. Box A represents immediately prior to reperfusion while box B represents 1 hr after reperfusion. *$P < 0.05$ vs. control. (b) Relative change in the aortic end diastolic pressure in the IABP-Pre, IABP-Post, and the control groups. Aortic end diastolic pressure compared between groups over the course of reperfusion. Box A represents immediately prior to reperfusion. *$P < 0.05$, IABP-Pre vs. control; †$P < 0.05$, IABP-Post vs. control; ‡$P < 0.05$, IABP-Pre vs. IABP-Post. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

pressure at reperfusion in the pre-IABP group vs. both the control and the post-IABP groups (Fig. 1b, box A). Similarly, the rate pressure product was reduced with counter-pulsation at the time of reperfusion in the pre-IABP group and continued during reperfusion in both IABP groups vs. control (Table II).

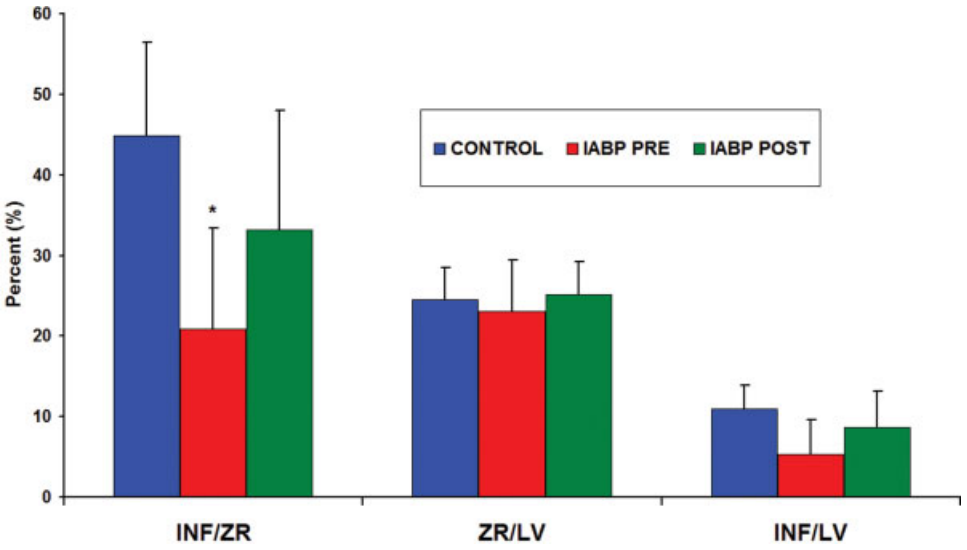

Fig. 2. Percent infarction of the LV in the IABP-Pre, IABP-Post, and the control groups. Infarction size (INF) as a percentage of the zone at risk (ZR) and as a percentage of the left ventricle (LV) (±1 SD). *$P < 0.05$, IABP-Pre vs. control. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE III. Regional Myocardial Blood Flow

	Absolute flows (mL/g/min)		
	Control	IABP Pre	IABP Post
Baseline			
Control region	0.99 ± 0.18	0.76 ± 0.13	0.74 ± 0.04
Ischemic region	0.88 ± 0.16	0.71 ± 0.13	0.74 ± 0.09
LAD occlusion (25 min)			
Control region	0.75 ± 0.14	0.76 ± 0.13	0.54 ± 0.08
Ischemic region	0.05 ± 0.01	0.04 ± 0.01	0.06 ± 0.07
Reperfusion (5 min)			
Control region	0.65 ± 0.07	0.67 ± 0.16	1.02 ± 0.30
Ischemic region	1.87 ± 0.42	1.53 ± 0.43	2.36 ± 0.50
Reperfusion (4 hr)			
Control region	1.03 ± 0.08	0.87 ± 0.16	0.77 ± 0.24
Ischemic region	1.05 ± 0.26	0.63 ± 0.15	0.72 ± 0.34

Values are expressed as means ± SEM. Regional myocardial blood flow from inner two-thirds of the ischemic and non-ischemic areas showing no statistical difference in the blood flow to the ischemic area to account for the difference in infarct size.

Effect of IABP on Infarct Size

A summary of infarct size data in control, pre, and post animals is shown in Fig. 2. The ZR was constant among all groups. No differences were noted in the ZR to LV weight ratio (ZR/LV), or infarct weight to total weight of the LV (INF/LV). The infarct size expressed a percentage of ZR in control animals was 44.9% ± 4.8%. In the IAPB-Pre group there was a 53% reduction in infarct size to 20.9% ± 5.1% ($P < 0.05$) compared with reperfusion alone. In the IABP-Post group, the infarct size was intermediate compared with the other two groups at 33.2% ± 6.1% ($P = 0.16$ vs. control group).

Effect of IABP on Myocardial Blood Flow

RMBF, expressed as mL/min/g, was measured in the area of coronary occlusion as well as in the contralateral area (Table III). Baseline blood flow to the inner two-thirds of the myocardium in the ischemic and nonischemic regions was similar for all three groups. Ischemic zone myocardial blood flow measured after 25 min of coronary occlusion indicated a severe and comparable level of ischemia for all groups. There were no significant differences in flow in the non ischemic region during occlusion. At 5 min reperfusion, blood flow to the inner two-thirds of the myocardium in the ischemic region was not significantly different comparing all three groups, as well as the transmural RMBF. Hyperemic flow was noted in all three groups, with the IABP-Pre group displaying a trend toward lower flow. At 4 hr, reperfusion flows were not significant between the three groups in the ischemic and nonischemic areas in the inner 2/3 and transmural RMBF; however, there was a trend of lower flow in the IABP-Pre group. The ischemic to nonischemic ratios between the groups RMBF at baseline, occlusion, 5 min reperfusion, and 4 hr reperfusion were not significant comparing all three groups.

Effect of IABP on Plasma ET-1 Levels

A trend of lower transcardiac release of ET-1 in the IABP-Pre group animals was seen compared with the IABP-Post animals and controls at 15 min, 30 min, and 1 hr of myocardial reperfusion. The CS sampling minus the aortic sampling plasma levels of ET-1 in pg/100 μL are shown in Fig. 3. The results were not significant

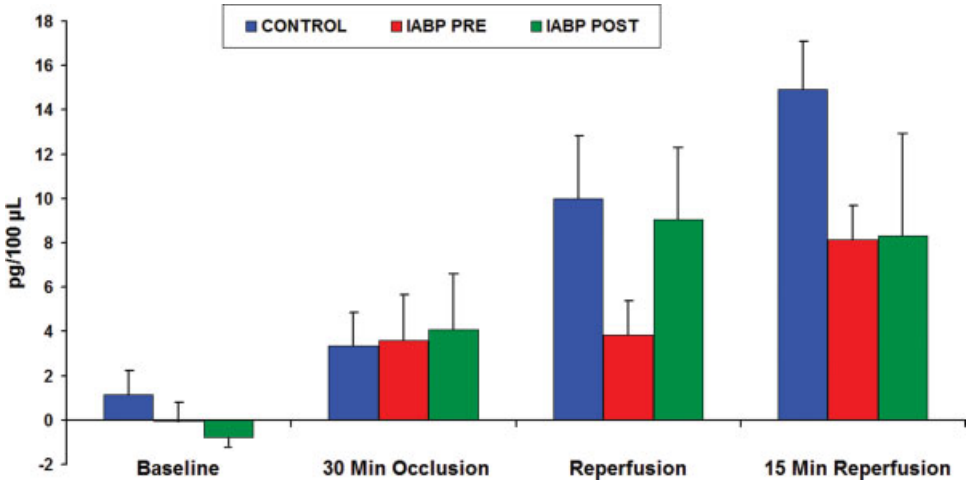

Fig. 3. Transcardiac endothelin-1 release during reperfusion. Coronary sinus–aortic endothelin-1 (ET-1) levels for the three groups showing the trend for decreased ET-1 release during reperfusion under the protection of LV unloading. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

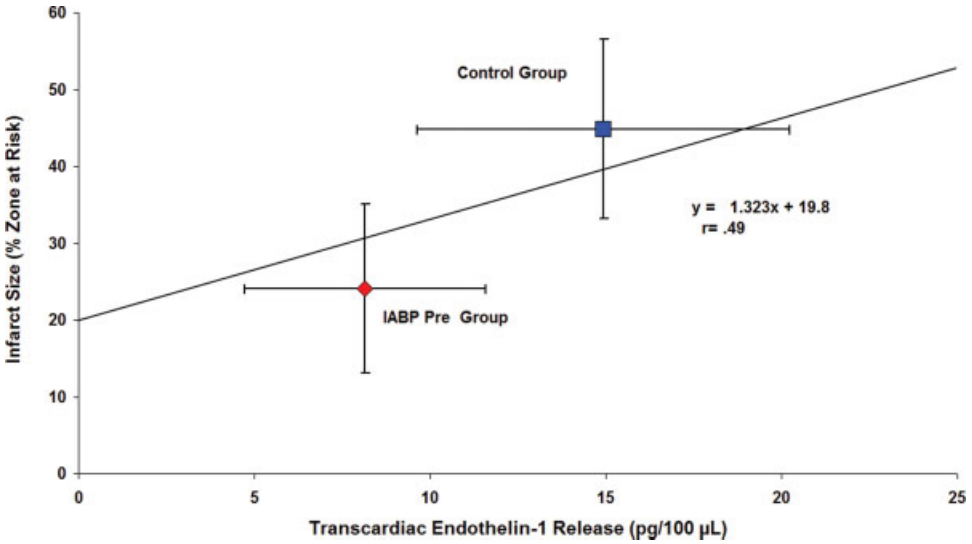

Fig. 4. Change in infarct size related to endothelin-1 release 15 min after reperfusion. Transcardiac endothelin-1 (ET-1) release is more in animals with larger infarct sizes. When broken down by groups, the IABP-Pre group had smaller infarct sizes and less transcardiac ET-1 release (P = 0.01). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

using ANOVA with a means comparison test at each time point sampled. To assess the relationship between ET-1 release and infarct size, independent of any intervention, we analyzed this relationship for the total group of tested animals. There is a correlation between infarct size and ET-1 release at 15 min of reperfusion, regardless of animal treatment (r = 0.59). Using ANCOVA with infarct sizes compared with ET-1 levels at 15 min reperfusion as the covariate the IABP-Pre was significant (P = 0.01, r = 0.49) compared with the control group using Newman–Keuls means comparison test (Fig. 4). The IABP-Pre group vs. IABP-Post group (P = 0.16) and the IABP-Post group vs. control group (P = 0.08) results were not significant.

DISCUSSION

We have demonstrated, for the first time, a reduction in infarct size with partial LV unloading using a commercially available IABP in porcine infarct model. This reduction in infarct size was not due to alterations in RMBF which were not altered by IABP usage. The

reduction in infarct size must be attributable to the altered hemodynamics at the time of reperfusion in the IABP-Pre animals. The amount of LV unloading obtained by the IABP was sufficient to reduce the amount of endothelin-1 release by ischemic myocardium which was correlated with a reduction in infarct size.

For optimal myocardial salvage, the left ventricle must be unloaded prior to reperfusion. In most clinical trials looking for benefit of LV unloading with IABPs, the IABP is placed after reperfusion. The PAMI II trial, a large multicenter randomized trial, designed to determine the role of prophylactic IABP after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction, showed that the IABP strategy conferred modest benefits in reduction of recurrent ischemia (13.3% vs. 19.6%, $P = 0.08$) compared with conservative management. The IABP neither did it result in a decrease in the rates of infarct-related artery reocclusion, or reinfarction, nor did it promote myocardial recovery and improved overall clinical outcome. However, virtually all patients enrolled in the PAMI II trial received the IABP unloading after restoration of infarct-related artery blood flow by direct angioplasty [6]. Brodie et al. showed in the setting of cardiogenic shock or high-risk myocardial infarction that IABP placement prior to revascularization reduced the number of episodes of ventricular fibrillation, cardiopulmonary arrest, or prolonged hypotension in the catheterization laboratory compared with IABP placement after revascularization or without revascularization [5]. Using cardiac magnetic resonance imaging, Lima and coworkers showed only accelerated recovery of systolic function using IABP started after reperfusion in a canine infarct model. There was no difference in myocardial salvage in the IABP group compared with control [22]. These data are consistent in showing the benefit of LV unloading with an IABP in the setting of acute myocardial infarction can only be obtained if the left ventricle is unloaded at the time of reperfusion.

In addition, we have developed one possible mechanism through which the IABP decreases infarct size by altering the amount of ET-1 release. Several experimental studies demonstrated increased circulating plasma levels and myocardial tissue content of ET-1 during myocardial ischemia [23–25]. The efficacy of a variety of ET receptor antagonists in the treatment of ischemic-reperfusion injury has been demonstrated in several different animal models [26–28]. Morawietz et al., on the other hand, showed that an ET-A receptor was markedly upregulated in failing human myocardium and that this increased ET-A expression was not affected by angiotensin-converting enzyme inhibitor treatment but was normalized by LVAD unloading [29]. Although the precise mechanism remains to be determined, ET-1 plays a critical role in determining the extent of reperfusion injury in cardiac myocytes.

Limitations

(1) Our model is an acute open-chest experiment in an anesthetized animal and may not accurately reflect findings in intact awake animals. (2) The relatively brief period of reperfusion may not represent what occurs later in regards to infarct healing. (3) The potential effect of blood loss during acute open-chest experiments can only be partially accounted for by the fact that all groups had similar surgical insults.

Possible Clinical Applications

Findings in this study suggest the need for additional clinical trials of the only widely available LV assist device for this clinical setting. Reperfusion injury not only occurs in humans, but also can be decreased with LV unloading prior to reperfusion. There have been numerous other methods attempted to limit reperfusion injury from preconditioning, to free-radical scavengers to, most recently, pacing-induced dyssynchrony [30], but none have emerged as clinically efficacious. We have previously shown similar benefits with more substantial LV unloading using an assist device in an animal model [6]. LV unloading with the IABP holds the promise for significantly reducing the risk of reperfusion injury when initiated immediately prior to reperfusion in high-risk STEMI patients.

CONCLUSIONS

LV unloading with an IABP prior to reperfusion reduces the extent of myocardial necrosis in porcine hearts subjected to 1 hr of LAD artery occlusion and 4 hr of reperfusion compared with either reperfusion alone or LV unloading after reperfusion. Inhibition of myocardial ET-1 release by LV unloading may be a significant mechanism of myocardial protection. These data suggest that in high-risk STEMI patients, IABP unloading prior to reperfusion might be more beneficial than IABP placement postreperfusion.

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