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Basic Science Review

Mechanical Left Ventricular Unloading Prior to Reperfusion Reduces Infarct Size in a Canine Infarction Model

Hela Achour, MD, Fernando Boccalandro, MD, Patricia Felli, James Amirian, Margaret Uthman, MD, Maximillian Buja, MD, and Richard W. Smalling,* MD, PhD

We tested the hypothesis that unloading the left ventricle just prior to reperfusion provides infarct size reduction compared with left ventricular (LV) unloading postreperfusion and reperfusion alone. Twenty-four mongrel dogs were subjected to 2 hr of left anterior descending artery occlusion and 4 hr of reperfusion. A transvalvular (TV) left ventricular assist device (LVAD) was inserted just prior to reperfusion and maintained during the rest of the experiment (LV Assist Pre group). In the LV Assist Post group, the TV LVAD was inserted and activated just after reperfusion. A control group was subjected to reperfusion alone with a sham-TV LVAD. At baseline, the hemodynamic data were similar in the three groups. Myocardial infarct size expressed as percentage of area at risk was significantly reduced in the LV Assist Pre group compared to the control group ($P = 0.011$) and to the LV Assist Post group ($P < 0.05$). At 4 hr of reperfusion, transmural myocardial blood flow in the ischemic zone was slightly higher in the animals unloaded prior to reperfusion compared to controls and significantly higher than in the LV Assist Post group ($P = 0.04$). Postreperfusion end-diastolic wall thickness returned to baseline level in the TV LV Assist Pre group compared to both controls and TV LV Assist Post group. In these latter two groups, a significant increase in postreperfusion end-diastolic wall thickness and contraction band necrosis in the central ischemic zone correlated well with the degree of reperfusion injury. LV unloading prior to, but not after, reperfusion reduces the extent of myocardial necrosis in canine hearts subjected to 2 hr of left anterior descending artery occlusion and 4 hr of reperfusion compared to either reperfusion alone or LV unloading after reperfusion. *Catheter Cardiovasc Interv 2005;64:182–192.*

Key words: acute myocardial infarction; reperfusion injury; left ventricular unloading; transvalvular axial flow device

INTRODUCTION

In patients with acute ST segment elevation myocardial infarction, early reperfusion (< 6 hr after onset of pain) is a prerequisite for limiting the extent of myocardial damage [1–3]. However, reperfusion per se can be deleterious, especially in patients presenting beyond 3 hr after onset of ischemia [4,5].

We have previously demonstrated that a transvalvular (TV) left ventricular assist device (LVAD) developed by Wampler et al. [6] improved collateral blood flow to the ischemic myocardium and resulted in a significant reduction in infarct size when used throughout the period of coronary occlusion and reperfusion in a canine acute myocardial infarction model [7,8]. Mechanical left ventricular (LV) unloading immedi-

Division of Cardiology, University of Texas at Houston Medical School and Memorial Hermann Hospital, Houston, Texas

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*Correspondence to: Dr. Richard W. Smalling, Department of Internal Medicine, Division of Cardiology, University of Texas at Houston Medical School, 6431 Fannin, MSB1.246, Houston, TX 77030. E-mail: richard.w.smalling@uth.tmc.edu

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TABLE I. Hemodynamic Parameters in Control and Unloaded Animals*

		LAD occlusion				Reperfusion						
	Baseline pump off	10-min pump off	1-hr pump off	2-hr pump off	2-hr pump 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
Heart rate (bpm)												
Control	108 ± 13	100 ± 7	98 ± 9	95 ± 10	95 ± 10	89 ± 7[a]	89 ± 7	87 ± 6[a]	84 ± 4[a]	80 ± 6[a]	81 ± 7[a]	81 ± 7[a]
LVAD post	116 ± 21	115 ± 20	116 ± 19	114 ± 21	114 ± 21	110 ± 17	106 ± 17	107 ± 18	109 ± 22	109 ± 21	108 ± 23	106 ± 20
LVAD pre	111 ± 16	104 ± 17	104 ± 18	98 ± 17	95 ± 18[b]	91 ± 17[b]	91 ± 17[b]	92 ± 15[b]	91 ± 17[b]	88 ± 10[b]	88 ± 18[b]	85 ± 12[b]
Mean arterial pressure (mm Hg)												
Control	114 ± 19	104 ± 18	109 ± 17	109 ± 13	109 ± 13	104 ± 13	104 ± 13	104 ± 13	104 ± 13	104 ± 15	102 ± 16	102 ± 16
LVAD post	106 ± 13	102 ± 15	102 ± 14	101 ± 18	101 ± 18	94 ± 16	95 ± 14	104 ± 18	96 ± 22	90 ± 23	93 ± 16	84 ± 16
LVAD pre	105 ± 11	110 ± 13	112 ± 12	114 ± 15	112 ± 21	111 ± 16	111 ± 16	114 ± 21	118 ± 16*	116 ± 20*	109 ± 21	106 ± 25
Systolic left ventricular pressure (mm Hg)												
Control	126 ± 18	111 ± 18	117 ± 16	117 ± 13	117 ± 13	112 ± 13	112 ± 13	112 ± 13	113 ± 14	112 ± 16	111 ± 17	111 ± 17
LVAD post	118 ± 10	113 ± 13	112 ± 12	111 ± 16	111 ± 16	104 ± 16	101 ± 22	110 ± 21	103 ± 25	96 ± 20	100 ± 19	94 ± 28
LVAD pre	118 ± 13	120 ± 13	122 ± 13	123 ± 16	119 ± 20	114 ± 16	114 ± 16	115 ± 20	116 ± 25	120 ± 20*	112 ± 24	120 ± 25
End-diastolic left ventricular pressure (mm Hg)												
Control	5 ± 2	11 ± 3	12 ± 5	10 ± 2	10 ± 2	13 ± 4	13 ± 4‡	12 ± 5	9 ± 3	10 ± 2	10 ± 3	10 ± 3
LVAD post	6 ± 3	10 ± 3	9 ± 2	9 ± 3	9 ± 3	10 ± 2	8 ± 3	8 ± 3	7 ± 4	7 ± 4	7 ± 3	9 ± 4
LVAD pre	6 ± 2	11 ± 3	11 ± 3	10 ± 3	9 ± 4	10 ± 4	10 ± 4	9 ± 2	9 ± 2	9 ± 3	9 ± 4	11 ± 4
End-diastolic wall thickness (mm)												
Control	11.9 ± 4	10.3 ± 4	10.0 ± 4	10.0 ± 4	10.0 ± 4	12.8 ± 4	12.8 ± 4	13.0 ± 4	12.9 ± 4	12.7 ± 4	12.4 ± 3	12.4 ± 3[a]
LVAD post	15.1 ± 3	13.8 ± 3	13.7 ± 3	13.8 ± 3	13.8 ± 3	16.7 ± 4	17.0 ± 4	16.8 ± 3	16.6 ± 3	16.5 ± 3	17.2 ± 3	17.0 ± 3
LVAD pre	11.7 ± 3	10.0 ± 1	9.9 ± 1	9.9 ± 1	10.1 ± 1	11.5 ± 3	11.5 ± 3	11.3 ± 2	11.2 ± 2	11.4 ± 3	11.5 ± 3	11.1 ± 2[b]
RPP												
Control	134 ± 24	113 ± 19	117 ± 20	113 ± 19	113 ± 19	100 ± 18	100 ± 18	98 ± 15	95 ± 12	91 ± 17	91 ± 17	90 ± 19
LVAD post	135 ± 32	129 ± 34	130 ± 30	127 ± 36	127 ± 36	112 ± 30	106 ± 32	118 ± 34	113 ± 40	106 ± 37	110 ± 35	100 ± 32
LVAD pre	132 ± 28	124 ± 27	126 ± 26	122 ± 28	114 ± 30	106 ± 27	106 ± 27	110 ± 31	114 ± 33	107 ± 23	105 ± 36	103 ± 31

[a]$P < 0.05$ LV Post vs. control.

[b]$P < 0.05$ LV Pre vs. LV Post.

*Data are reported as mean ± SD. HR, heart rate (beats/min); MAoP, mean aortic pressure (mm Hg); LVEDP, left ventricular end diastolic pressure (mm Hg); MAP, mean atrial pressure (mmHg); RPP, rate-pressure product (mmHg beats/min/100). There were no significant differences in HR, MAoP, MAP, left ventricular pressure, or in the rate-pressure product between the control, LV Assist Pre, or LV Assist Post groups during baseline. However, at the end of the occlusion and during reperfusion, the LV Assist Post group had significantly higher HRs and lower MAoPs. These differences, however, did not result in a significantly different rate-pressure product between the three groups. There was a modest decrease in the LVSP with left ventricular assistance ($P = 0.11$). Left ventricular unloading resulted in a significant decrease in the LVEDP when compared to controls ($P = 0.03$).

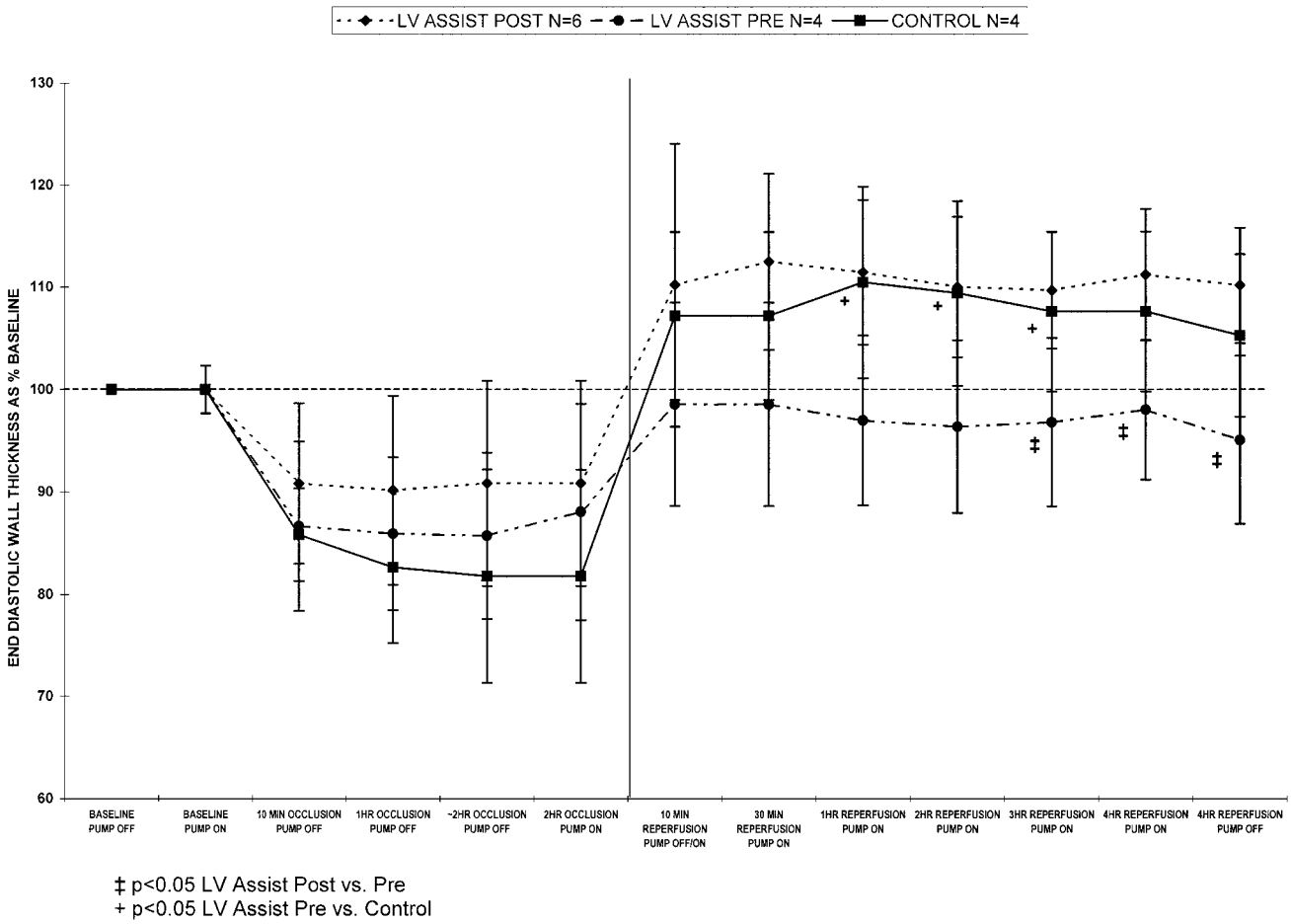


Fig. 1. Ischemic zone end-diastolic wall thickness expressed as a percentage of baseline in the three groups of dogs. At baseline, EDWT of the risk area was similar in the three groups. At 10 min postreperfusion, wall thickness increased to 12.8 ± 4 and 16.7 ± 4 mm in controls and LV Assist Post animals, which corresponds to 7% and 10% rises in ischemic regional EDWT in the two groups, respectively. In animals unloaded prior to and during the reperfusion period, ischemic regional myocardial wall thickness did not increase over baseline at 10 min of reperfusion and thereafter and remained lower than that of controls and LV Assist Post animals.

ately prior to and during reperfusion, a more clinically relevant scenario, has not been previously tested. Clinical experience in treating high-risk patients with acute myocardial infarction has suggested that mechanical LV unloading after reperfusion does not impact mortality favorably [9].

This experimental model of an acute myocardial ischemia followed by reperfusion has been designed to test the hypothesis that LV unloading, just prior to and during reperfusion, will limit the increase in reperfusion-related end-diastolic wall thickness (EDWT) and contraction band necrosis (CBN) in the central ischemic region, a marker of reperfusion injury that would result in a significant reduction in infarct size when compared to LV unloading after reperfusion and reperfusion alone.

MATERIALS AND METHODS

Studies were carried out in 24 conditioned mongrel dogs of either sex weighing 28–35 kg. The study protocol was approved by the Ethical Committee for Laboratory Animals of the University of Texas at Houston Medical School; all the experiments were performed according to the committee's guidelines.

Surgical Preparation

The animals were anesthetized and instrumented as previously described [10]. The dogs were injected with 3,000 units of heparin just prior to TV LVAD insertion. The TV LVAD (Medtronic) was inserted through a 20 Fr introducer sheath placed in the femoral artery and advanced under fluoroscopic control into the LV.

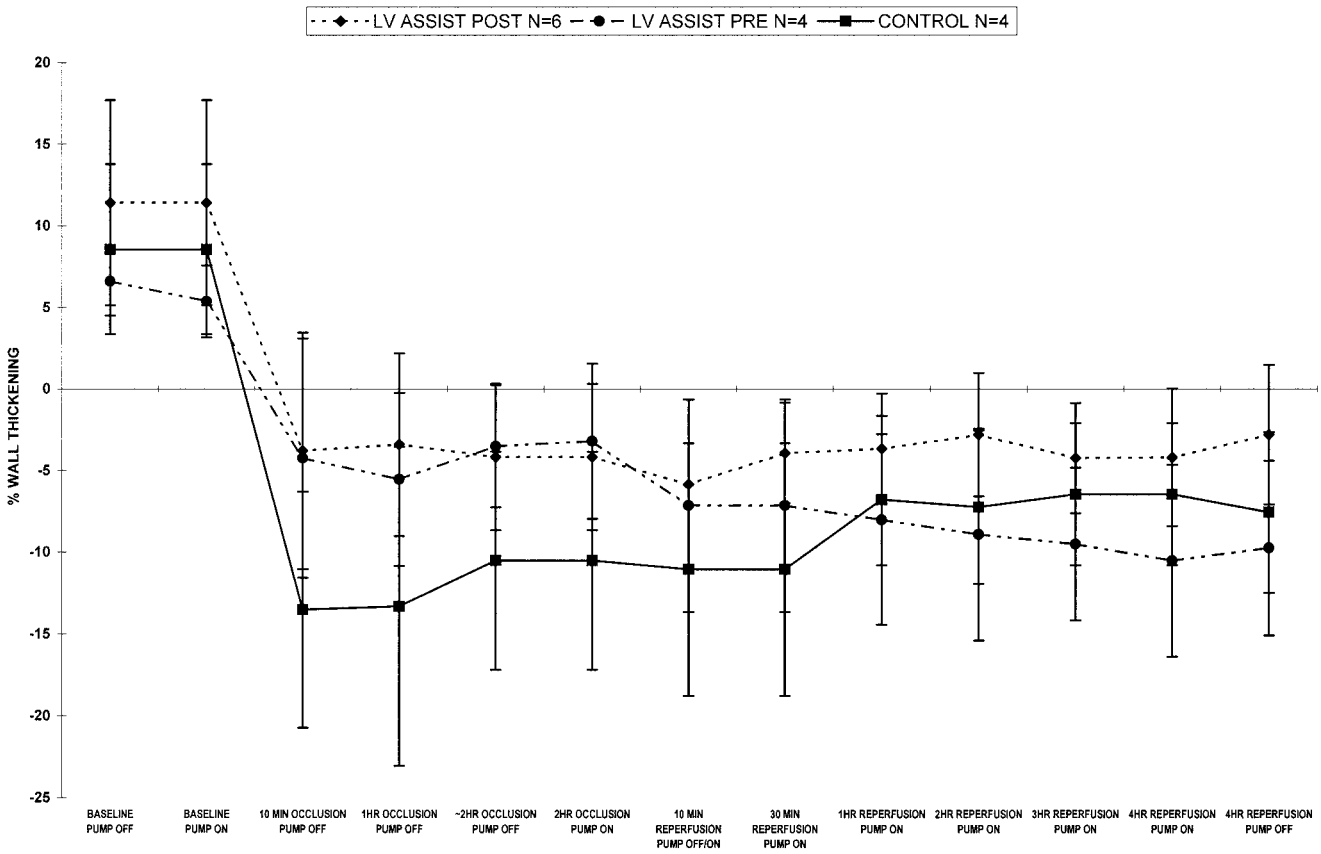


Fig. 2. Systolic wall thickening in the LAD distribution with and without LV assistance. During LAD occlusion, there was a marked decrease in the systolic wall thickness in the ischemic region in all three groups. With reperfusion, there was an increase in the systolic wall thickness in the LAD territory. No statistically significant difference was noted between the three groups.

Maximum flow was used (2–3 l/min, depending on mean arterial pressure and LV filling pressure) in supported animals.

Dogs were randomized into three groups of eight animals each. In the TV LV Assist Pre group, mechanical unloading was initiated 15 min prior to reperfusion and maintained during the whole period of reperfusion. In the LV Assist Post group, mechanical unloading was initiated 15 min after reperfusion and continued for the rest of the experiment. The control group consisted of sham-TV LVAD insertion and reperfusion alone.

Experimental Protocol

Baseline measurements included hemodynamic values (arterial blood pressure, LA pressure and LV pressure), regional myocardial blood flow (RMBF), regional end-diastolic segment length and thickness, and segmental shortening in the left anterior descending artery (LAD) region. Hemodynamic and functional measurements were recorded continuously throughout the experiment on a Gould chart recorder (Thermo-Spectra). Three to five million 15 μm radioactive microspheres (NEN-TRAC, DuPont) were injected in a volume of 1 ml through the LA catheter over 30 sec, followed by 10 ml of normal saline. During the microsphere injection, arterial blood was continuously withdrawn from the ascending aorta for a period of 2 min with the use of a Harvard pump. RMBF was determined according to the method of Heymann et al. [11].

Following baseline measurements, a snare was tightened around the LAD to occlude it and flow cessation was documented by Doppler flow signal. Hemodynamic and functional measurements were repeated at 10 min, 1 hr, and 1 hr 45 min postocclusion. Radioactive microspheres were injected at 2 hr just prior to reperfusion. The occluder was then released and reflow was reestablished and documented using the Doppler flow probe. The above hemodynamic measurements were repeated at 10 min, 30 min, 1 hr, 2 hr, and 3 hr in all three groups with and without LV assistance. Radioactive microspheres were injected at 4 hr postreperfusion. The TV LVAD was then pulled above the aortic arch with a reduced-rate support setting and final hemodynamic and functional measurements were taken

TABLE II. Myocardial Blood Flow in Control and Unloaded Animals*

		LV Assist Pre group			
	Control group	Off	On	*P*	LV Assist Post group
Transmural myocardial blood flow absolute flows (ml/g/min)					
Baseline					
Control region	0.64 ± 0.29	0.70 ± 0.13	0.89 ± 0.43	NS	0.69 ± 0.09
Ischemic region	0.61 ± 0.33	0.64 ± 0.12	0.64 ± 0.18	NS	0.57 ± 0.18
LAD ischemia					
Control region	0.71 ± 0.26	0.69 ± 0.22	0.65 ± 0.28	NS	0.69 ± 0.15
Ischemic region	0.04 ± 0.06	0.05 ± 0.03	0.17 ± 0.23	NS	0.03 ± 0.03
Reperfusion (4 hr)					
Control region	0.57 ± 0.10	0.85 ± 0.58			0.77 ± 0.30
Ischemic region	0.35 ± 0.18	0.57 ± 0.32		[a]	0.23 ± 0.22
Subepicardial blood flow absolute flows (ml/g/min)					
Baseline					
Control region	0.59 ± 0.26	0.69 ± 0.17	0.83 ± 0.32	NS	0.64 ± 0.15
Ischemic region	0.60 ± 0.28	0.68 ± 0.18	0.71 ± 0.27	NS	0.54 ± 0.16
LAD ischemia					
Control region	0.63 ± 0.26	0.74 ± 0.25	0.53 ± 0.14	NS	0.60 ± 0.16
Ischemic region	0.09 ± 0.16	0.03 ± 0.03	0.15 ± 0.18	NS	0.06 ± 0.04
Reperfusion (4 hr)					
Control region	0.57 ± 0.14	0.95 ± 0.77		NS	0.76 ± 0.35
Ischemic region	0.36 ± 0.23	0.61 ± 0.38		NS	0.34 ± 0.18
Subendocardial blood flow absolute flows (ml/g/min)					
Baseline					
Control region	0.69 ± 0.34	0.71 ± 0.13	0.95 ± 0.50	NS	0.74 ± 0.07
Ischemic region	0.65 ± 0.42	0.62 ± 0.13	0.62 ± 0.19	NS	0.58 ± 0.22
LAD ischemia					
Control region	0.78 ± 0.30	0.74 ± 0.25	0.71 ± 0.34	NS	0.73 ± 0.19
Ischemic region	0.02 ± 0.02	0.03 ± 0.03	0.14 ± 0.20	NS	0.02 ± 0.03
Reperfusion (4 hr)					
Control region	0.58 ± 0.08	0.08 ± 0.45		NS	0.77 ± 0.22
Ischemic region	0.43 ± 0.21	0.59 ± 0.30		[a]	0.17 ± 0.22

[a]$P < 0.05$ LV Assist Pre vs. LV Assist Post.

*RMBF with and without LV assistance was measured at baseline, 2 hr of occlusion, and 4 hr of reperfusion. During baseline and LAD ischemia, no differences in the ischemic region absolute RMBF was noted between the three groups. At 4 hr of reperfusion, the LV Assist Pre group had significantly higher-risk region blood flows than that of controls and animals unloaded after reperfusion ($P < 0.05$). There were no changes in MBF in the control areas throughout the experiment.

10 min prior to sacrifice. Infarct size quantification using the triphenyl tetrazolium chloride (TTC) staining was measured according to the method of Fishbein et al. [12].

Light Microscopy and Electron Microscopy

Quantitative analysis of CBN by light microscopy. The areas of each histological myocardial section (excluding epicardium and endocardium) were measured in pixels by an image analysis system (Olympus Microsuite Software/Biological System; Soft Imaging System, Lakewood, CO) [13]. The numbers of myofibrils with CBN were normalized to 100 mm^2. These lesions ranged from a few to hundreds of myofibrils per section.

Electron microscopy. Tissue samples taken from the central ischemic and posterior nonischemic zones were perfused and fixed with 3% glutaraldehyde in 0.1 M phosphate buffer. After thorough rinsing, the tissue was postfixed in osmium tetroxide, dehydrated, and embedded in epoxy resin. A minimum of 2–4 transmural sections were obtained from the noninvolved area at risk and infarcted areas from each heart. The electron micrographs were evaluated for signs of myocyte injury, including changes in the nuclei, mitochondria, myofilaments (CBN) sarcolemma, and the presence of edema and extravasated erythrocytes.

Data Analysis

Results were expressed as mean ± SD. For multiple comparison procedures, including hemodynamic and coronary flow data, ANOVA and Newman-Keul's multiple-range tests were performed for repeated measures (Statistica). ANCOVA was performed to compare infarct size in the TV LVAD pre- and postreperfusion as well as control groups, with collateral flow used as a covariate. A P value of < 0.05 was considered significant.

RESULTS

Effects of LV Unloading on Hemodynamics

Hemodynamic parameters during baseline, ischemia, and reperfusion for the TV LVAD and control dogs are shown in Table I. At baseline, there were no significant hemodynamic differences between the three groups. LV unloading produced consistent declines in left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP) whether initiated before or after reperfusion. For comparison, hemodynamic groups were combined into unloaded animals (with pump activation immediately before or after reperfusion) and compared to controls. LVEDP fell significantly with pump activation compared to sham-operated animals ($P = 0.03$). Initiation of the TV LVAD resulted in a small nonsignificant decline in LVSP ($P = 0.11$). Although these changes were relatively modest, they resulted in a significant decrease in heart rate (HR) in supported animals compared to controls ($P = 0.03$). Similarly, the rate-pressure product decreased significantly from 117.3 ± 28.7 to 110.4 ± 30.1 (mm Hg × bpm/100; $P = 0.004$) with unloading compared to no changes in the controls.

LV Unloading, Regional End-Diastolic and Systolic Wall Thickening

At baseline and during occlusion, the EDWT of the area at risk was not significantly different in the three groups studied. At 10 min postreperfusion, wall thickness increased to 12.8 ± 4 and 16.7 ± 4 mm in controls and LV Assist Post animals, which corresponds to 7% and 10% rises in ischemic regional EDWT in the two groups, respectively. In animals unloaded prior to and during reperfusion, myocardial thickness did not rise above baseline at 10 min postreperfusion. At 1 hr of reperfusion and thereafter, in the LV Assist Pre group, ischemic regional EDWT was and remained significantly lower than that of controls ($P \leq 0.01$ vs. control) and LV Assist Post group ($P \leq 0.01$ vs. LV Assist Post; Fig. 1). There was no statistically significant difference in ischemic regional systolic myocardial wall thickness between the three groups (Fig. 2).

Effect of LV Unloading on RMBF Analysis

Myocardial blood flow, expressed in ml/min/g, was measured in the ischemic and nonischemic areas. Flows are shown subepicardially, subendocardially, as well as transmurally (Table II). There was no difference in the ischemic RMBF at baseline and during ischemia between the three groups. At 4 hr of reperfusion, the subendocardial and the transmural flows were significantly higher in the LV Assist Pre group compared to LV Assist Post group and controls ($P < 0.05$; Table II). There were no changes in RMBF in the control areas throughout the experiment.

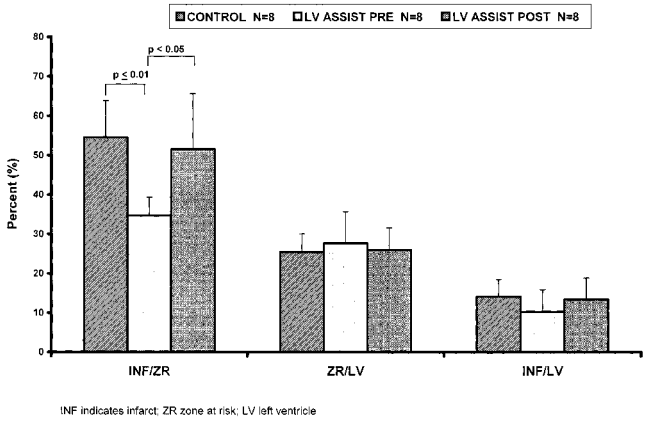


Fig. 3. Bar graph demonstrating INF/ZR and risk region and infarct zone as a percentage of the LV for the TV LVAD and control groups. Only early unloading with the TV LVAD resulted in a statistically decreased INF/ZR ($P = 0.011$ vs. control; $P \leq 0.05$ vs. LV Assist Post).

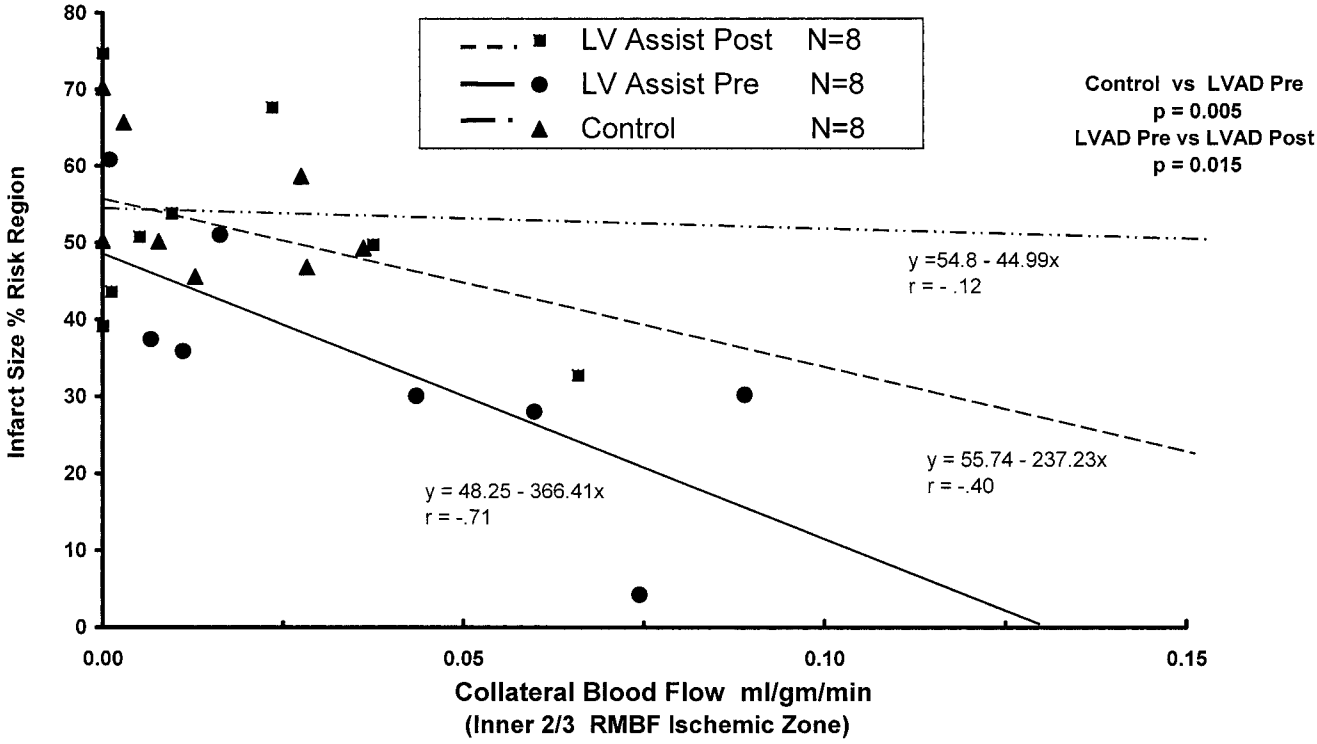
Effect of LV Unloading on Infarct Size

Only early unloading with the TV LVAD resulted in a statistically decreased infarct-to-zone at risk ratio (INF/ZR; 34.69 ± 4.62% for LV Assist Pre vs. 54.58% ± 9.23% for controls, $P = 0.011$, and vs. 51.51% ± 14.04% for LV Assist post, $P < 0.05$; Fig. 3). INF/ZR was not reduced in the LV Assist Post group, and INF/ZR analyzed on a region-by-region basis was significantly lower in all regions of the myocardium, including endocardium, mid myocardium, epicardium, and transmural in the LV Assist Pre animals. No differences between the groups were noted in the zone at risk to LV weight.

Infarct size expressed as a percent of zone at risk was compared between the groups with collateral blood flow as a covariate in the inner 2/3 of the ventricular wall (Fig. 4) as well as transmurally. Only early LV unloading resulted in a statistically significant decreased ratio of INF/ZR at a given level of collateral blood flow. The correlation coefficient of the LV Assist Post group was −0.40 in the subendocardium and myocardium, but −0.51 when transmural flow was examined. The LV Assist Pre group enhanced this effect with an $r = -0.71$ in the inner 2/3 and $r = -0.56$ transmurally. This trend was significant for the LV Assist Pre vs. either control (ANCOVA, $P \leq 0.005$ inner 2/3; $P \leq 0.01$ transmurally) or LV Assist Post (ANCOVA, $P \leq 0.015$ inner 2/3; $P \leq 0.029$ transmurally group).

Infarct Size as Function of EDWT

Figure 5 demonstrates the regression line between the ischemic zone EDWT when expressed as a percen-



RMBF indicates regional myocardial blood flow; LV Assist Pre, left ventricular assist device pre-reperfusion; LV Assist Post, left ventricular assist device post-reperfusion; INF/ZR, infarct zone expressed as a percentage of zone at risk.

Fig. 4. Relationship between mean RMBF and infarct size as a percentage of LV area at risk in the inner 2/3 of the myocardium during LAD occlusion. Only early LV unloading (LV Assist Pre reperfusion) resulted in a statistically decreased INF/ZR at a given level of MBF (P = 0.011 vs. control; $P \leq 0.05$ vs. LV Assist Post).

tage of baseline at 10 min postreperfusion and the INF/ZR. There was a good correlation between the percent change (from baseline to 10 min after reperfusion) in EDWT and the amount of myocardial necrosis in the ischemic region (r = 0.69).

Electron Microscopy and Histopathological Results

Representative data from each group are shown in Figure 6. All three groups of animals had comparable control region histology. The CBN was multifocal in the TV LV Assist Post group (n = 3), with mild and focal interstitial edema and slight hemorrhage. In the TV LV Assist Pre group (n = 3), occasional myocytes with hypercontracted myofibrils, mild interstitial edema, or extravasation of red blood cells were seen in the ischemic region. The control group (n = 3) showed severe cell injury with multifocal hypercontraction of myofibrils in the ischemic region. Animals with increased postreperfusion EDWT had extensive CBN in the risk region vs. near normal ultrastructure in dogs with no increase in postreperfusion myocardial wall thickness.

DISCUSSION

We have demonstrated that mechanical unloading of the LV just prior to and during reperfusion dramatically improves infarct salvage and prevents the increase in the EDWT over that seen with reperfusion alone or TV LVAD support postreperfusion. Infarct size and INF/ZR in the LV Assist Post group remained as large as that of the control group despite the continuation of mechanical unloading throughout reperfusion. This suggests that timing of the initiation of mechanical assistance is of paramount importance for maximizing infarct salvage in subjects undergoing mechanical reperfusion therapies for evolving myocardial infarction. In our model, postreperfusion myocardial wall thickness in the ischemic region was significantly increased in controls and LV

Assist Post group as opposed to animals unloaded prior to reperfusion. The increase in EDWT above control levels at reperfusion was associated with CBN seen on electron microscopy (EM) in the risk region and larger infarcts. Animals unloaded prior to reperfusion had no increase in postreperfusion EDWT in the ischemic region, smaller infarcts, and rare CBN.

Haendchen et al. [14] showed that no significant recovery of LV function was seen in the center of the ischemic zone when the early reperfusion EDWT in this segment increased by more than 25%, and there was almost total recovery of function when the early reperfusion increase in segmental EDWT was less than 10%. They showed recovery in function up to 7 days after reperfusion in ischemic segments. In contrast, in this study and in view of the stunning that occurs after ischemia, we did not demonstrate any significant difference in the ischemic zone systolic wall thickening between the three groups. It might be worthwhile in the future to do longer follow-up studies to determine if LV unloading prior to reperfusion improves late functional recovery and if there is a correlation with postreperfusion myocardial wall thickness in the ischemic region and late recovery of systolic function. In a separate but similar study comparing LV unloading prior to reperfusion and sham-unloaded dogs subjected to 2 hr of LAD occlusion and 4 hr of reperfusion, we demonstrated that the ischemic region of the control animals (n = 2) had greater degree of CBN with disrupted sarcolemma as compared to the unloaded animals (n = 2; data not shown). It has been reported that, in human acute myocardial infarction, CBN is seen diffusely in the outer third of the LV wall in the heart recanalized by coronary thrombolysis and is rare in patients in whom recanalization is not achieved during coronary thrombolysis [15]. Contraction bands are secondary to hypercontracture of myocytes resulting from massive calcium influx early at reperfusion. Although the association between massive calcium influx and molecular ischemia/reperfusion injury has been established, the source of the elevated intracellular calcium remains controversial and may have important therapeutic significance.

In previous studies, we compared a similar TV LVAD with intra-aortic balloon pump counterpulsation (IABP) and reperfusion alone in a canine model of myocardial infarction [16]. We demonstrated that it improved collateral blood flow to the ischemic myocardium, was superior to the IABP in LV unloading and circulatory support, and was associated with a significant reduction in infarct size when used throughout the period of coronary occlusion. Such a scenario is not clinically relevant since there is always a delay in initiation of therapy after onset of pain in acute myocardial infarction patients. Several large trials evaluating the effect of IABP counterpulsation in patients undergoing direct angioplasty for myocardial infarction found no benefit of the balloon pump unloading [17,18]. In the Primary Percutaneous Transluminal Coronary Angioplasty in Acute Myocardial Infarction (PAMI II) trial, a large multicenter randomized study designed to determine the role of prophylactic IABP counterpulsation after PTCA in acute myocardial infarction, the IABP strategy conferred modest benefits in reduction of recurrent ischemia (13.3% vs. 19.6%; $P = 0.08$) compared to conservative management. The IABP did not 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 [18]. However, virtually all patients enrolled in the PAMI II trial received IABP unloading after restoration of infarct-related artery blood flow by direct angioplasty [18]. Allen et al. [19] previously showed that for significant infarct salvage to occur, LV unloading must occur prior to reperfusion. However, Allen et al. [19] used cardiopulmonary bypass, which is a different model of ventricular decompression compared to the TV LVAD and is not widely clinically available. Additionally, Allen et al. [19] did not correlate the effects of LV unloading with histopathological data.

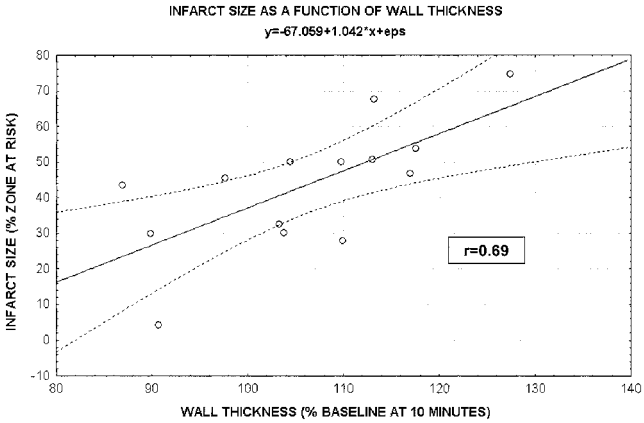


Fig. 5. Linear regression between the ischemic zone EDWT expressed as a percentage of baseline at 10 min postreperfusion and the extent of INF/ZR. The ischemic zone EDWT at 10 min postreperfusion correlated well with the amount of myocardial necrosis (r = 0.69).

Matsumoto et al. [20] reported that in a canine acute myocardial infarction model, the LV unloading effect of LVAD support increases RMBF and subsequently limited reperfusion injury and infarct size. Unfortunately, Matsumoto et al. [20] did not analyze infarct size with collateral flow as a covariate. The currently accepted way to avoid collateral blood flow artifact is to employ an analysis of variance against the infarct sizes with the myocardial blood flow (MBF) as a covariate [21]. In our study, when transmural MBF was used as a covariate according to the method of Reimer

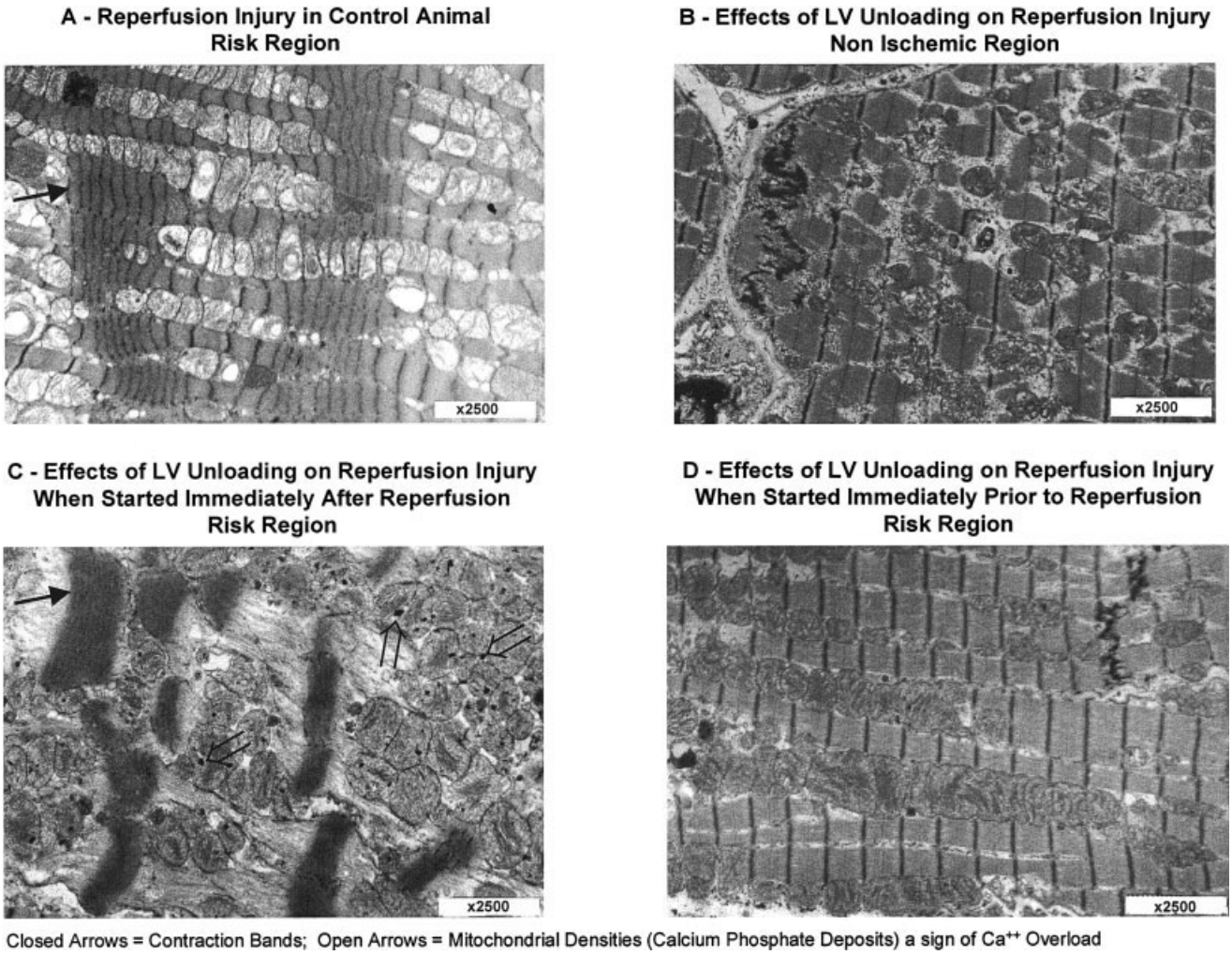


Fig. 6. Effect of the TV LVAD on coronary occlusion and reperfusion in dogs. EM findings. A: In the control ischemic region, the cardiomyocytes exhibit multifocal hypercontraction of myofibrils indicative of severe cell injury. B: In the control nonischemic region, there was a normal ultrastructure. C: When initiated after reperfusion, the TV LVAD resulted in severe myocyte injury with prominent CBN. D: When the TV LVAD was initiated prior to reperfusion, there was an overall generally normal ultrastructure.

et al. [21], INF/ZR was significantly smaller in the animals unloaded prior to reperfusion compared to controls and the TV LV Assist Post group. The regression lines for both treated groups were found to be parallel, but the LV Assist Pre group line was significantly displaced downward. This suggests that even though MBF may play a pivotal role in infarct salvage by LV unloading, this is not the sole mechanism of myocardial salvage by LV unloading. Consistent with our findings, Meyns et al. [22] demonstrated in a sheep ischemia reperfusion model that partial LV support with a modest decrease in preload resulted in a significant reduction in infarct size without any measured increase in myocardial perfusion in the ischemic area.

It has been suggested that the extent of necrosis after an ischemic insult is related to myocardial oxygen consumption [23], and thus modification of intracavitary LVSP, a major determinant of myocardial oxygen consumption, can directly affect infarct size. In our experimental model, although the decline in the LVSP in both unloaded groups was quite modest and not significantly different between the two treated groups, there was a reduction in infarct size only in the group of animals unloaded prior to and during reperfusion.

Study Limitations

The findings provide evidence that LV unloading prior to reperfusion results in a reduction in infarct size in a

canine ischemia/reperfusion model. However, this may be due to limitations in the study's design, which includes a different model of LAD occlusion and reperfusion using snare ligation and release compared to the human ischemia reperfusion model. These uncertainties make it difficult to extrapolate the results of this study to humans. Additional research in humans and in a variety of animal models evaluating multiple endpoints is required to determine whether LV unloading before reperfusion limits infarct size.

We found that, one, unloading the LV just prior to reperfusion with a TV LVAD following a 2-hr LAD occlusion resulted in significant infarct salvage when compared to both controls and LV Assist Post group. Two, unloading the LV just after reperfusion produced no significant improvement in infarct salvage when compared to reperfusion alone. Three, postreperfusion ischemic regional EDWT returned to baseline level in the animals unloaded immediately prior to reperfusion compared to both controls and LV Assist Post group. Four, animals with increased EDWT early after reperfusion had extensive CBN in the risk region, which correlated with larger infarcts, suggesting that EDWT in the ischemic zone after reperfusion may be a useful tool for assessing the efficacy of infarct salvage strategies.

Clinical Implications

These experimental data and the clinical experience of Brodie et al. [24] suggest that in primary or rescue percutaneous transluminal coronary interventions, initiating IABP support and LV unloading prior to restoring infarct-related artery flow in high-risk patients with ST segment elevation myocardial infarction may emerge as an effective adjunctive measure to protect against reperfusion injury.

In our catheterization laboratory, instituting IABP support routinely takes less than 5 min, which is a small incremental delay compared to 3–4 hr after onset of pain, which typically elapses prior to balloon inflation in patients presenting with acute MI.

This experimental work and that of Meyns et al. [22] also suggest that relatively modest LV unloading is beneficial and needs to be tested in clinical trials either using IABP with appropriate timing of initiation or a LV assist device, which could unload more vigorously than the IABP but which could still be inserted quickly and percutaneously.

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