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Lymphatic Diversion Prevents Myocardial Edema Following Mesenteric Ischemia/Reperfusion

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ABSTRACT

Objective: Mesenteric ischemia/reperfusion (I/R) is associated with cardiac dysfunction. Mesenteric lymph primes polymorphonuclear leukocytes (PMNs) for increased superoxide release following I/R. We hypothesized that mesenteric I/R causes myocardial edema resulting in myocardial dysfunction, and that diverting mesenteric lymph would preserve myocardial function.

Methods: Two canine groups were studied: lymphatic diversion (LD) and no lymphatic diversion (No LD). Preload recruitable stroke work, $\pm dp/dt_{max}$, isovolumic relaxation (tau), cardiac output, and myocardial water content (MWC) were determined. I/R consisted of 60 min of ischemia followed by 180 min of reperfusion. Myocardial myeloperoxidase (MPO) was measured as an index of PMN leukosequestration. In addition, mesenteric lymph harvested after I/R was infused into normal *canines* and all variables measured.

Results: MWC increased from baseline in No LD. Tau and $-dp/dt_{max}$ were significantly affected in No LD, but not in LD. After mesenteric I/R, mesenteric lymph primed PMNs for increased superoxide production. Lymph diversion resulted in significantly lower myocardial MPO. With reinfusion of I/R lymph, MWC and tau increased. MPO was also increased post I/R mesenteric lymph reinfusion.

Conclusions: Our data indicate that myocardial dysfunction after mesenteric I/R is due to lymph-induced, PMN-mediated microvascular alterations and myocardial edema.
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KEY WORDS: myocardial edema, mesenteric lymph, mesenteric ischemia/reperfusion

INTRODUCTION

Mesenteric ischemia/reperfusion (I/R) commonly arises in critically ill patients either as part of an underlying disease including hypovolemic shock, burns, or endotoxemia (3,15,22), or as a consequence of surgical intervention such as aortic surgery (18). These patients frequently develop myocardial dysfunction compromising their survival. Numerous studies have shown that pulmonary injury is associated with mesenteric I/R (8,9,23). The pulmonary injury is thought to be initiated by lymph draining the injured gut, priming polymorphonuclear leukocytes (PMNs) for increased oxygen-derived free radical release that then attack the pulmonary microvasculature (1,23). In vitro studies suggest that this lymph also may be directly toxic to pulmonary endothelium (1,9).

We reasoned that the heart also serves as a target of PMN-mediated injury following mesenteric I/R. If primed PMNs did attack the myocardial microvascular exchange barrier, then myocardial edema may develop. We and others have shown that myocardial edema is associated with left ventricular systolic and diastolic dysfunction (6,19). Accordingly, the myocardial dysfunction following mesenteric I/R may be due to an injured cardiac microvasculature. Thus, we hypothesized that mesenteric I/R would result in myocardial edema and left ventricular dysfunction via

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a PMN-mediated mechanism. We also hypothesized that in the presence of mesenteric I/R, diverting mesenteric lymph away from the circulatory system for external collection would reduce myocardial edema and preserve left ventricular function. To test our hypotheses, we studied the effects of mesenteric I/R with and without lymph diversion on left ventricular function and myocardial edema. In a separate experiment, the effects of infusion of post-I/R mesenteric lymph into normal dogs were also studied.

METHODS

Animal Preparation

All procedures were approved by the University of Texas Animal Welfare Committee and were consistent with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals" (NIH publication 85-23, revised 1985). Conditioned mongrel dogs ($n = 13$) of either sex were anesthetized by intravenous administration of 25 mg/kg thiopental sodium (Pentothal, Abbott Laboratories, North Chicago, IL), and underwent tracheal intubation and mechanical ventilation with 100% oxygen using a volume-cycled respirator (Siemens-Elema AB, Syndbyberg, Sweden). Anesthesia was maintained with intravenous infusion of 1% thiopental sodium in Ringer's solution. Temperature was maintained using a heating blanket.

Fluid-filled catheters were placed into the left femoral artery and vein and connected to pressure transducers for arterial pressure monitoring, arterial blood sampling, and fluid administration, respectively. A 7F Swan-Ganz thermodilution catheter was inserted into the pulmonary artery via the right jugular vein for pressure and cardiac output measurements. Umbilical tape was placed around the inferior vena cava for cardiac preload manipulation. A micromanometer-tipped pressure transducer (Millar Instruments Inc., Houston, TX) was introduced into the left ventricular cavity through the apex. Sonomicrometry crystals (10 MHz, Sonometrics, London, ON, Canada) were placed in the left ventricular (LV) subendocardium across the septum/free-wall and apex/base axes of the LV. The crystals were then connected to a sonomicrometer (Sonometrics, London, ON, Canada) for signal processing.

Mesenteric Lymphatic Cannulation and Mesenteric Ischemia/Reperfusion

A midline laparotomy was used to gain access to the peritoneal cavity. The cisternae chylae was cannulated with silastic tubing with distal ligation. The lymphatic cannula was connected to a calibrated pipette placed level with the lymphatic vessel. Timing the movement of the meniscus allowed calculation of lymph flow rate. Lymph and plasma protein concentrations were determined using a refractometer as described previously (5). Mesenteric lymphatic protein clearance was determined by multiplying lymph flow rate and lymph protein concentration. Atraumatic vascular clamps were used to occlude the mesenteric vessels, and with application, the distal mesenteric arteries lost all pulsation and the bowel serosa became a characteristic pale white color. The abdomen was covered with Saran wrap throughout the experiment after instrumentation.

Hemodynamics and Preload Recruitable Stroke Work

Systolic function was determined using preload recruitable stroke work (PRSW) and $+dp/dt_{max}$ indexed to left ventricular end-diastolic volume (LVEDV). The diastolic isovolumic relaxation time constant (tau) and $-dp/dt_{max}$ were used as measures of diastolic function. Hemodynamic data were simultaneously logged into a Macintosh Quadra 700 computer via an analog-to-digital data acquisition device (MacLab, World Precision Instruments Inc., New Haven, CT). Cardiac output was determined in duplicate by injecting 10 mL ice-cold Ringer's solution. Mean arterial pressure and pulmonary artery pressure/pulmonary artery occlusion pressure were measured with arterial catheters interfaced to pressure transducers. LV pressure was measured with a micromanometer (Millar, Houston, TX), and the left ventricular septum/free-wall and apex/base lengths were obtained with a sonomicrometer. These data were recorded at a frequency of 200 Hz during 10 seconds of inferior vena cava occlusion (Sonolab/Sonoview®, Sonometrics, London, ON, Canada). Using a 2-axis ellipsoid model measuring the apex-base and ant-post distances (mm), the LV volume (V_{LV}) can be calculated from the following equation:

$$V_{LV} = \pi \cdot (\text{apex-base})(\text{ant-post})(\text{ant-post}/6)\ [\text{mL}] \quad (1)$$

Preload recruitable stroke work was calculated as the slope of the relationship between LV end-diastolic volume and LV stroke work (SW) from

pressure-volume loops obtained using inflow occlusion of the inferior vena cava. SW was calculated as

$$SW = SV \cdot (MEP\text{-}EDP)\ [mL \cdot mm\ Hg] \qquad (2)$$

where SV is the LV stroke volume, MEP is the LV mean ejection pressure, and is measured from ejection onset to end ejection. Ejection onset was defined at 10 ms after the time of $+dp/dt_{max}$, and end ejection was defined at the time of $-dp/dt_{max}$. EDP is the LV end-diastolic pressure. The time constant for isovolumic relaxation, tau, was measured in msec. All measurements were taken in duplicate.

Myocardial and Ileal Water Content Determination

Myocardial and ileal water content for edema quantification was measured using a microgravimetric technique as previously described (5,6). With a biopsy needle (Tru-Cut®, Baxter Healthcare Corp., Deerfield, IL) transmyocardial biopsies were taken from the LV anterior or antero-lateral wall. Full thickness ileal biopsies were obtained with scissors, and the biopsy site was sutured closed. The specific density of these samples was measured in a linear density gradient consisting of bromobenzene and kerosene. Knowing myocardial/ileal specific density, the gram water per gram tissue or myocardial/ileal water content (MWC or IWC) can be calculated using the following equation:

$$MWC = \{1 - [(SG_{myo} - 1)/(1 - 1/SG_{dry}) \cdot SG_{myo}]\} \cdot 100\ [\%] \qquad (3)$$

where SG_{myo} and SG_{dry} are the specific gravities of the myocardial (or ileal) sample and of dry myocardium/ileum, respectively. At the end of the experiment, dogs were euthanized and the hearts/ileum rapidly excised, after which both ventricles/ileum were weighed and dried to a constant weight at 60°C. We calculated SG_{dry} using the equation

$$SG_{dry} = 1/\{1 - [(SG_{myo} - 1) \cdot W/(D \cdot SG_{myo})]\}\ [g] \qquad (4)$$

where W and D are wet and dry weights of both ventricles or ileum. We assumed that SG_{dry} did not change over time. Measurements were performed in triplicate.

PMN Priming/Superoxide Production

Naive PMNs were isolated using a Percoll based centrifugation (Polymorphprep) and resuspended in phosphate buffered saline glucose (PBSG) to ultimately yield 3.75×10^5 PMNs/microplate well. Mesenteric lymph was stored at −20°C after collection. Mesenteric lymph was incubated (5% final concentration) with naive PMNs for 5 minutes (23). The lymph/PMN mixture was then centrifuged at 300 g for 3 minutes at 37°C. The lymph supernatent was aspirated and the PMN pellet was resuspended in PBSG. PMNs were then aliquoted to the wells of the microplate with PBSG. Wells were filled with 133.5 ul (80 uM) of cyt C (Sigma, St Louis, MO), 15 ul PMN and 1.5 ul of fMLP (1 uM) + 1.5 μl PAF (2 uM). All reagents were kept at 37°C in a water bath, and reactions were at 37°C. A kinetic microplate reader (ThermoMax Kinetic Microplate Reader; Molecular Devices, Menlo Park, CA) and SoftMax software were used to determine superoxide Vmax, (nmol $O_2^-/3.75 \times 10^5$/min) based on the rate of change in absorbance of cytochrome *c* due to oxidation from superoxide production (10,23). Absorbance was measured every 20 seconds for 10 minutes. The rate of change was determined by calculating the slope of the change in OD, using the extinction coefficient of 8.4×10^{-3} L mol^{-1} min^{-1} for the 150 ul reaction volume and 550 nm wavelength. All assays were performed in duplicate to quadruplicate.

Myeloperoxidase Assay

A second group of animals ($n = 10$; 5/group) underwent the same protocol as outlined above. These animals were used to harvest myocardial tissue for myocardial myeloperoxidase (MPO) measurements. At the conclusion of the experiment, animals were sacrificed, and myocardial tissue harvested from the LV wall was frozen at −70°C. This tissue was then analyzed for MPO content as a measure of PMN leukosequestration in the myocardium. The methods of Bradley and Mullane were used for the analysis, and the data were expressed in IU MPO/100 mg tissue (4,17).

Experimental Protocol

Animals were randomized into lymph diversion (LD) or no lymph diversion (No LD) groups. Animals without lymph diversion underwent laparotomy with all procedures except lymphatic cannulation. There was a 30-minute period of stabilization

after instrumentation, followed by baseline measurements and collection of tissue samples. Measurements were made at 30-minute intervals. Mesenteric ischemia/reperfusion was initiated as detailed above.

I/R Lymph Reinfusion Study

In a separate experiment ($n = 7$), we sought to determine if reinfusing mesenteric lymph harvested from *canines* after I/R into healthy, non-injured animals would reproduce the myocardial performance changes, leukosequestration, and edema noted in the previous No LD group. After baseline measurements, the I/R lymph (128 ± 13 ml) was reinfused via the IVC catheter over one hour. Myocardial performance data and myocardial water content were determined as described above. Myocardial tissue was harvested for MPO assay at the conclusion of the procedure.

Analysis of Data

All data presented are mean ± SEM. Data analysis was carried out using Statistica software (StatSoft, Inc.). Time courses of each measured parameter were examined using analysis of variance (*ANOVA*) for repeated measures and Fisher's LSD. Between group time point comparisons were made using Student's t-test for unpaired data. A value of $p \leq 0.05$ was considered significantly different.

RESULTS

Myocardial performance data are shown in Table 1. A statistically significant prolongation of the isovolumic relaxation constant, tau, occurred in the No LD group but not in the LD group. Similarly, $-dp/dt_{max}$ decreased significantly in the No LD group compared to baseline but not in the LD group. Both groups demonstrated a decrease in cardiac output at 180 minutes after reperfusion (R-180). This is typical of anesthetized preparations over time. The decline in cardiac output occurred with maintenance of baseline central venous pressure, pulmonary capillary wedge pressure, and LVEDV. There were no significant decreases in myocardial contractility as measured by PRSW or $+dp/dt_{max}$ corrected for LVEDV.

Table 1. Myocardial performance following mesenteric ischemia and reperfusion

$n = 13$	Baseline	I−30 min	I−60 min	R−60 min	R−120 min	R−180 min
CO ($L \cdot min^{-1}$)						
LD	2.8 ± 0.2	2.5 ± 0.2	2.5 ± 0.2	2.5 ± 0.3	2.4 ± 0.3	1.9 ± 0.3*
No LD	2.3 ± 0.5	2.3 ± 0.5	2.3 ± 0.2	1.9 ± 0.4	1.8 ± 0.4	1.4 ± 0.3*
MAP (mm Hg)						
LD	112 ± 8	113 ± 8	114 ± 6	110 ± 5	104 ± 12	100 ± 11
No LD	122 ± 5	123 ± 7	109 ± 7	105 ± 7	95 ± 5	94 ± 9*
CVP (mm Hg)						
LD	7 ± 0	8 ± 0	7 ± 0	7 ± 0*	8 ± 1	8 ± 0
No LD	8 ± 0	8 ± 0	8 ± 0	9 ± 0	8 ± 0	8 ± 0
PCWP (mm Hg)						
LD	10 ± 1	11 ± 1	11 ± 1	9 ± 2	11 ± 2	13 ± 1
No LD	11 ± 1	11 ± 1	10 ± 1	11 ± 1	11 ± 1	12 ± 1
PRSW (mL·mm Hg)						
LD	74 ± 12	53 ± 3	57 ± 4	61 ± 13	62 ± 10	63 ± 15
No LD	69 ± 13	55 ± 5	68 ± 10	69 ± 11	62 ± 13	63 ± 13
Tau (ms)						
LD	41 ± 4	43 ± 2	50 ± 3	46 ± 2	46 ± 5	52 ± 5
No LD	38 ± 3	45 ± 5	48 ± 6	50 ± 9	44 ± 4	57 ± 11*
$-dp/dt_{max}$ ($mm\ Hg \cdot s^{-1}$)						
LD	2070 ± 249	1607 ± 140	1638 ± 190	1638 ± 122	1496 ± 266	1421 ± 171
No LD	2452 ± 366	2027 ± 200	1826 ± 252	1586 ± 218	1460 ± 249*	1364 ± 328*
dp/dt_{max}/EDV ($mm\ Hg \cdot s^{-1} \cdot mL^{-1}$)						
LD	23 ± 6	16 ± 2	17 ± 4	23 ± 3	25 ± 3	27 ± 5
No LD	22 ± 3	25 ± 6	25 ± 6	27 ± 7	23 ± 3	21 ± 4

CO—cardiac output, MAP–mean arterial pressure, CVP—central venous pressure, PCWP—pumonary capillary wedge pressure, PRSW—preload recruitable stroke work, Tau-isovolumic relaxation time constant, LD—lymphatic diversion, No LD—no lymphatic Diversion. Values are mean ± SEM, $^*p < 0.05$ compared to baseline.

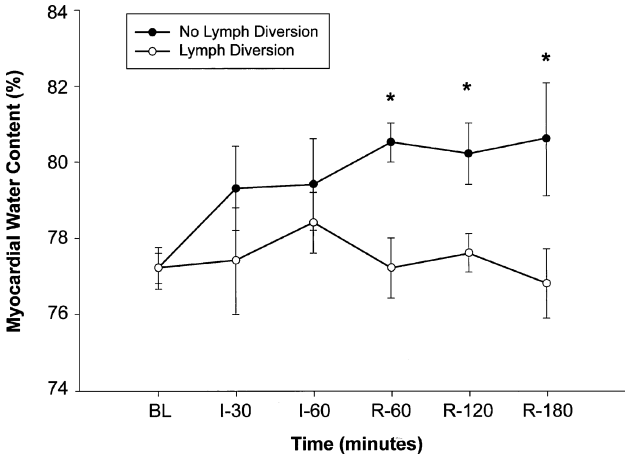

Figure 1. Myocardial water content (edema) is significantly greater with no lymph diversion compared to lymph diversion and baseline. "*" $p < 0.05$.

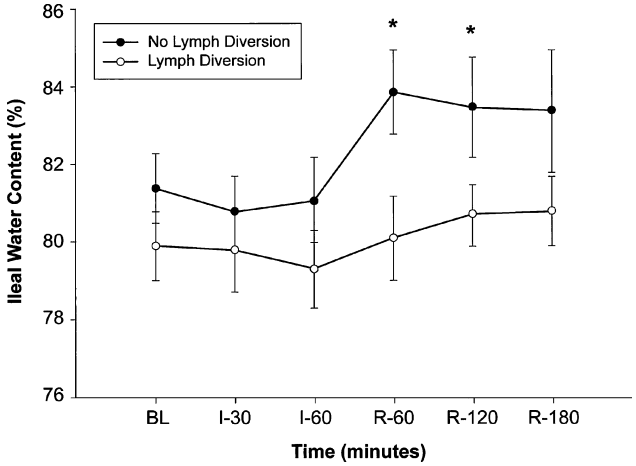

Figure 2. Ileal water content (edema) increases significantly following reperfusion with no lymph diversion compared to lymph diversion. Lymph diversion prevents the development of ileal edema due to a reduction in lymphatic outflow pressure (cvp). "*" $p < 0.05$.

Any trending in these variables could be caused by intestinal lymph bypassing our point of cannulation and entering the circulation.

Myocardial water content is shown in Figure 1. Myocardial water content increased in the No LD group compared to baseline. There was statistically significant lower myocardial water content in the LD group at 60 through 180 minutes after reperfusion (R-60, R-120, and R-180) when compared to the No LD group.

Mesenteric Lymphatic Data

Ileal water content is shown in Figure 2. Ileal tissue water increased in the No LD group relative to baseline. There was a statistically significant difference between groups at R-60 and R-120. Lymphatic protein clearance is shown in Figure 3 and was increased relative to baseline after 120 and 180 minutes of reperfusion.

PMN Superoxide Release/PMN Priming by Mesenteric Lymph

The data demonstrating the effect of mesenteric lymph on PMN superoxide production are shown in Figure 4. The activating stimulus fMLP caused increased superoxide production after incubation with mesenteric lymph at 180 minutes after reperfusion (R-180) when compared to baseline (BL) lymph, suggesting a priming effect of post I/R lymph. Adding the priming stimulus PAF further augmented the PMN priming response at both BL and R-180 timepoints.

Myeloperoxidase Data

Myocardial tissue MPO (R-180 timepoint) was 0.58 ± 0.26 U/100 mg tissue in LD and was 4.4 ± 1.9 U/100 mg tissue in the No LD group ($p \leq 0.05$).

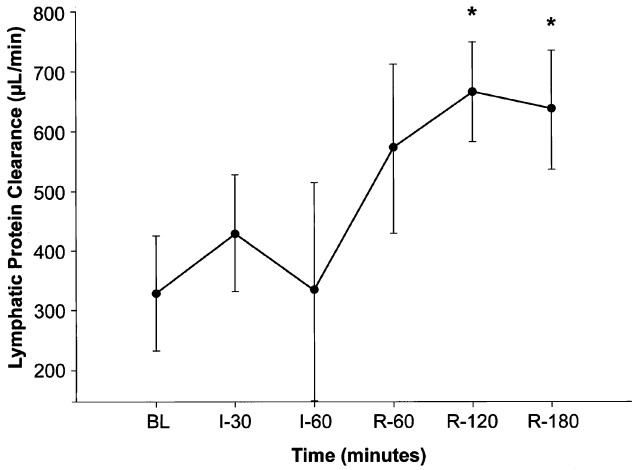

Figure 3. Mesenteric lymphatic protein clearance increases following ischemia reperfusion. "*" $p < 0.05$.

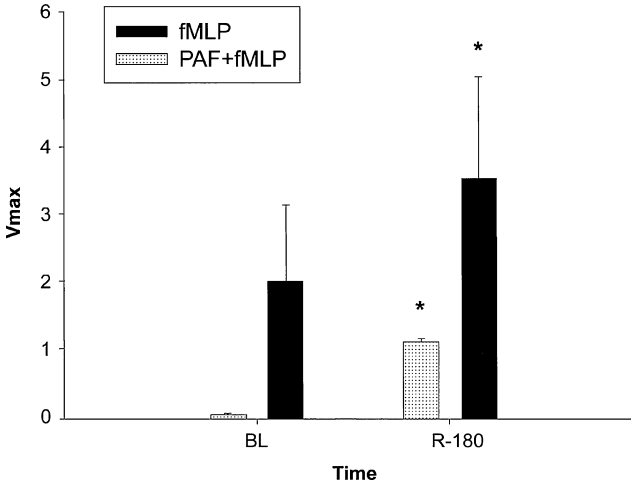

Figure 4. Post mesenteric I/R lymph primes PMNs for increased rate of superoxide production (Vmax). fMLP activates PMNs resulting in an increased rate of superoxide production at R-180 when compared to baseline (BL). The addition of the priming agent platelet activating factor (PAF) augments the priming response in both groups. Baseline and R-180 Vmax values are increased when compared to fMLP alone, suggesting further priming of the PMN by PAF or submaximal priming by mesenteric I/R lymph.

I/R Lymph Reinfusion Study

Myocardial performance data and myocardial water content are shown following I/R lymph reinfusion in Table 2. There was a significant prolongation of tau and decrease in $-dp/dt_{max}$ indicative of diastolic dysfunction. Myocardial water content increased from $75.7 \pm 0.3\%$ at baseline to $77.7 \pm 0.3\%$ at 180 min post reinfusion of I/R lymph. Myocardial tissue MPO was 5.6 ± 2.6 U/100 mg tissue at 180 minutes post reinfusion of I/R lymph.

DISCUSSION

Our data demonstrate that mesenteric ischemia/reperfusion results in myocardial edema and LV diastolic dysfunction. Moreover, mesenteric lymphatic diversion prevents myocardial edema and LV diastolic dysfunction, suggesting a reduction in myocardial microvascular insult. Supporting our hypothesis, reinfusion of I/R lymph reproduced the myocardial edema and LV diastolic dysfunction noted in the No LD group. Further, our data suggest a PMN-mediated mechanism for mesenteric I/R-induced myocardial dysfunction since post I/R mesenteric lymph primes PMNs and lymph diversion prevents myocardial PMN leukosequestration.

Two different potential mechanisms describing the damaging effects of post I/R mesenteric lymph on cardiopulmonary function have been proposed, namely direct toxic effects of lymph on the vascular endothelium and PMN-mediated vascular injury. Deitch and coworkers have demonstrated that mesenteric lymph is cytotoxic to human umbilical venous endothelial cells after hemorrhagic shock and resuscitation in rats (1,9). They have attributed this effect to a 100 kd complement dependent mediator that appears 1–3 hours after hemorrhagic shock in rats (1). Endotoxin and immune cell removal did not decrease the lymph cytotoxicity. In contrast, we did not find any significant toxicity after incubating mesenteric lymph at 1–10% final concentrations for between 4–18 hours with *canine* vascular endothelial cells from mesenteric or systemic venous beds (7). These differences may be due to the variable species responses, and/or the differences in hemorrhagic shock/resuscitation as opposed to isolated mesenteric I/R. Thus we believe that the more likely explanation for our results is mesenteric lymph priming of PMNs and vascular endothelium causing

Table 2. Myocardial performance data following mesenteric I/R lymph reinfusion

$n = 7$	Baseline	I—30 min	I—60 min	R—60 min	R—120 min	R—180 min
CO ($L \cdot min^{-1}$)	1.9 ± 0.1	1.8 ± 0.1	1.9 ± 0.2	1.6 ± 0.2	1.3 ± 0.3	1.2 ± 0.2
MAP (mm Hg)	124 ± 3	121 ± 1	117 ± 3	119 ± 4	121 ± 4	123 ± 5
CVP (mm Hg)	6 ± 1	7 ± 1	7 ± 0	7 ± 0	7 ± 0	7 ± 0
PCWP (mm Hg)	10 ± 0	10 ± 0	11 ± 0	10 ± 0	11 ± 0	12 ± 0
PRSW (mL·mm Hg)	63 ± 8	64 ± 6	66 ± 7	67 ± 8	66 ± 8	68 ± 7
Tau (ms)	35 ± 2	42 ± 3	37 ± 3	43 ± 3	48 ± 5*	48 ± 3*
$-dp/dt_{max}$ ($mm\ Hg \cdot s^{-1}$)	-2340 ± 92	-1914 ± 89	-1953 ± 89	-1888 ± 123	-1689 ± 147*	-1936 ± 155

CO–cardiac output, MAP–mean arterial pressure, CVP–central venous pressure, PCWP–pumonary capillary wedge pressure, PRSW–preload recruitable stroke work, Tau–isovolumic relaxation time constant, LD–lymphatic diversion, No LD–no lymphatic diversion. Values are mean ± SEM, $^*p < 0.05$ compared to baseline.

PMN adherence, transendothelial migration, and microvascular injury. Our data, as well as those of others, demonstrate that mesenteric lymph after hemorrhagic shock/resuscitation or mesenteric I/R result in PMN priming and subsequent cardiopulmonary PMN leukosequestration and injury. In all of these studies, lymph diversion prevents pulmonary injury (2,16,20,23). Our data are unique in that we have shown a pathophysiologic link between the mesenteric lymph, PMN priming/leukosequestration, and myocardial edema/dysfunction after mesenteric I/R.

Numerous potential mechanisms have been shown to play a role in the myocardial dysfunction associated with mesenteric I/R (11–14,21). Many studies point to the primed and subsequently activated PMN as the link between mesenteric I/R and myocardial dysfunction. In a series of studies using a Langendorff preparation, Horton and White demonstrated that mesenteric I/R caused myocardial contractile dysfunction due to lipid peroxidation/oxygen derived free-radical mediated myocardial injury (11,12). Data that suggest that the activated PMN is the source of cardiac injury after mesenteric injury are found in studies from Horton and White as well as Shahani et al. (21). Horton and White found that both plasma and heart tissue malonyldialdehyde concentrations increased after mesenteric I/R, and reversal of lipid peroxidation returned myocardial function to control levels. Using a similar model, Shahani et al. showed that mesenteric I/R increased myocardial myeloperoxidase and TNF-alpha. Furthermore, myocardial TNF-alpha synthesis has been shown to increase after shock and resuscitation (associated with mesenteric I/R). While TNF-alpha is a direct myocardial depressant, it also promotes leukosequestration. Taken together, these data suggest a pathophysiologic sequence of increased myocardial TNF-alpha production followed by proinflammatory mesenteric lymph entering the myocardial circulation. PMNs primed by mesenteric lymph could be activated by myocardial TNF-alpha resulting in lipid peroxidation and myocardial edema (microvascular barrier injury). Functionally, this is manifest as diastolic and/or systolic dysfunction as shown in our model as well as Horton's and Shahani's studies. Our data are consistent with the studies of Horton and Shanani in that mesenteric I/R causes myocardial PMN leukosequestration. Importantly, our study demonstrates that the mesenteric lymph carries proinflammatory stimuli associated with PMN priming, myocardial leukosequestration, myocardial edema, and dysfunction.

Our data demonstrate that mesenteric I/R causes ileal edema and increased lymphatic protein clearance both of which could imply increased microvascular permeability, surface area, or pressure (Figure 3). However, ileal edema did not develop in the LD group due to the reduction in pressure opposing lymphatic outflow from a central venous pressure of 6–9 mm Hg down to approximately zero. Reduction of the force opposing lymph flow by diversion serves to increase lymph flow. Augmented lymph flow is one of the classic anti- edema safety factors (increased lymph flow, increased interstitial pressure, and decreased interstitial oncotic pressure) noted in organs subjected to conditions that increase transvascular fluid filtration. Since cardiac lymphatics were not cannulated and thus continued to drain into the prevailing CVP, lack of cardiac edema is attributed to the absence of circulating factors removed by mesenteric lymph diversion.

There are some potential limitations to our study. The finding that LV systolic dysfunction did not occur despite the development of significant myocardial edema is different than other studies. Possible explanations include unrecognized autonomic stimuli that resulted in augmented contractility despite the development of myocardial edema. Abrupt changes in venous capacitance with clamping/declamping could result in increased autonomic output. However, the absence of heart rate change argues against the mechanism of increased autonomic tone.

In summary, we have demonstrated that mesenteric I/R causes myocardial edema and diastolic dysfunction mediated by mesenteric lymph. Diversion of the mesenteric lymph prevents the development of myocardial edema, dysfunction, and myocardial PMN leukosequestration. These data suggest that myocardial dysfunction after mesenteric I/R is due to PMN mediated myocardial microvascular changes resulting in edema.

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