

Renal Ischemia-Reperfusion Injury Does Not Induce Pulmonary Dysfunction in Sheep

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It has already been shown that pulmonary injury is induced after intestinal or hind limb ischemia-reperfusion injury. The purpose of this study was to determine the effect of renal ischemia-reperfusion injury on the pulmonary system. We compared the pulmonary effects of 60 and 90 minutes ischemia followed by 24 hour reperfusion in sheep kidneys. Standard hemodynamic measurements, arterial and mixed venous blood gas analysis, urine output, creatinine clearance, and blood urea nitrogen concentration were measured at baseline, during ischemia and reperfusion periods. After 24 hours of reperfusion, animals were sacrificed and underwent autopsy with collection of samples for wet/dry lung-weight ratio, lung tissue conjugated dienes, and renal histology. As expected, renal ischemia resulted in an increased serum creatinine and blood urea nitrogen concentrations, decreased creatinine clearance, and histological evidence of renal damage. There was no evidence of pulmonary hypertension or hypoxemia during renal ischemia-reperfusion. There was also no significant difference in the wet/dry lung-weight ratios or lung tissue conjugated dienes between the two ischemic groups (60 and 90 minutes) and nonischemic control group. These results suggest that renal ischemia-reperfusion injury was not associated with a significant degree of pulmonary dysfunction.

Key Words: Kidney, ischemia, reperfusion, pulmonary dysfunction, sheep

Since investigations were undertaken into the roles of xanthine oxidase (Granger *et al.* 1986) and granulocyte (Zimmerman and Granger. 1990) in ischemia-reperfusion injury, many other studies have shown that this injury is not localized to the ischemic and subsequently reperfused organ (Hammond *et al.* 1985; Klausner *et al.* 1989b, c, d). The means

by which ischemia-reperfusion injury is manifested in distant organs is related to neutrophil mediated oxygen free radical production. Previously, it has been shown that lower torso ischemia-reperfusion can induce pulmonary injury (Klausner *et al.* 1989d). Isolated gut ischemia-reperfusion, independent of endotoxin, has also been shown to contribute to the development of pulmonary injury after lower torso ischemia (Koike *et al.* 1994). The contribution of isolated renal ischemia-reperfusion to the development of lung injury after lower torso ischemia-reperfusion has not been previously explored. Although the kidney is a small organ, representing only 0.5% of total body weight, it receives approximately 25% of the cardiac output. Given this large blood supply, it is reasonable to assume that isolated renal ische-

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mia-reperfusion injury would result in the production of large amounts of toxic oxygen metabolites which may induce pulmonary dysfunction. The purpose of this study was to determine the contribution of kidney ischemia-reperfusion injury to pulmonary dysfunction.

MATERIALS AND METHODS

The experimental design and procedures described below were approved by the University of Texas Medical Branch-Galveston's Animal Care and Use Committee. During the course of this experiment, we adhered to the guidelines for the care and use of experimental animals as established by the National Institutes of Health.

Surgical preparation

Female sheep (n=18) of the Merino breed, weighing 26~44 kg, free of parasites and other infectious agents were prepared for study five days before experimentation. After overnight fasting, with free access to water, anesthesia was induced with 2~2.5% halothane in 100% O₂ via mask. Following induction, animals were endotracheally intubated and placed on mechanical ventilation. Under 1~1.5% halothane anesthesia and sterile conditions, a Swan-Ganz thermal-dilution catheter (model 93A-131-7F, Edward Laboratories, Palo Alto, CA, USA) was inserted into the pulmonary artery via the right external jugular vein. The right groin was prepared and draped in the usual sterile manner and an incision made over the right femoral vessels. The femoral artery and vein were isolated and Silastic catheters (Intracath[®], Becton/Dickinson, Sandy, Utah, USA) were placed in each vessel and advanced forward into the distal abdominal aorta and caudal vena cava, respectively. Then the animal was positioned and the right flank was prepared and draped in the usual sterile manner. Through a retroperitoneal approach, the right renal artery was identified and isolated. A pneumatic occluder (4 mm, Vascular Occluder, IVM, CA, USA) was placed around this renal artery near its origin from the aorta. The more distal portion of this artery was also isolated and

dissected free from surrounding tissues. A 4-mm transit time ultrasonic flow probe (Transonic Systems, Ithaca, NY, USA) was placed around this distal portion of the artery and sutured into place to prevent rotation. The flank incision was closed in layers using appropriate sutures. The animal was then repositioned and the above described procedure was applied to the left renal artery. The animal was allowed a five-day period to recover from the operation, during which it was monitored for adequate food, water intake, urine output, fever, and signs of postoperative pain. A urinary catheter was placed under ketamine anesthesia (1.5 mg/kg, IV), 24 hours prior to the start of the experiment.

Experimental design

Twelve sheep were then randomized and assigned to either a 60-minute (n=6) or 90-minute group (n=6) of bilateral renal ischemia, followed by 24 hours of reperfusion. The remaining six animals were utilized as non-ischemic controls. Standard hemodynamic measurements, arterial and mixed venous blood gas analysis, urine output, creatinine clearance, and blood urea nitrogen concentration were determined at baseline, during the ischemic period, and at 0.5, 1, 2, 4, 8, 16 and 24 hours after reperfusion. Renal ischemia was induced by inflation of bilateral renal artery pneumatic occluders with 4-5 ml of 0.9% NaCl. Confirmation of complete renal artery occlusion was obtained by a zero-flow reading by the ultrasonic flow probe. After completion of this protocol, animals were anesthetized with ketamine (1.5 mg/kg, IV) and sacrificed with 60 ml of saturated potassium chloride solution. Once death was confirmed by flat pressure trace for 10 minutes, autopsy was performed and samples collected for wet/dry lung-weight ratio, lung tissue conjugated dienes, and renal histopathology.

Standard hemodynamics, blood gas measurements, renal function, chemistries

Mean arterial, central venous, pulmonary artery, and pulmonary wedge pressures were measured using transducers (P23ID; Statham Gould, Oxnard, CA, USA) with a continuous heparinized flushing mechanism. The transducers were connected to an

OM9 physiologic recorder (Electronics for Medicine-Honeywell, Pleasantville, NY, USA) for graphic display of electronically calculated mean pressures. Cardiac output was determined by thermodilution technique utilizing a cardiac output computer (Model 9520, American Edwards Laboratories, Irvine, CA, USA). Ten ml of 5% dextrose solution at 4°C was used as the indicator.

Arterial and mixed venous blood gas analysis was determined using a blood gas analyzer and co-oxymetry (Instrumentation Laboratory BG3 and Co-oximeter 282, Milan, Italy).

The severity of renal injury was assessed at 4, 8, 16 and 24 hours after reperfusion by measuring serum creatinine, blood urea nitrogen, urine output, urine creatinine and creatinine clearance calculated by using the following formula. Creatinine clearance (ml/minutes) = urine volume (ml) X urine creatinine (mg/ml) / serum creatinine (mg/ml) / minutes.

Blood free wet/dry lung-weight ratio

Utilizing the entire right and left lower lung lobes, the blood free wet/dry lung-weight ratio was determined using the modified technique described by Pearce *et al.* (1965).

Lung tissue conjugated dienes assay

The procedure for measuring lung tissue conjugated dienes described by Till *et al.* (1985) was used.

Renal histology

Specimens of both right and left kidneys were harvested for light microscopy. These samples were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 4-mm intervals, and stained with hematoxylin and eosin as well as Leder's stain to extenuate the presence of neutrophils. All slides were interpreted by a pathologist blinded to the grouping of this experiment.

Tissue damage and neutrophil infiltration was evaluated using a semi-quantitative scale of 1+ to 4+, which was reflected by the increasing degree of ischemic damage and neutrophil infiltration, where 1+ meant minimal injury and 4+ meant severe injury

Table 1. Definition of terms for description of histologic changes after ischemic injury of kidney

Scale	ISCHEMIC INJURY
0	No detectable injury
+	Microscopic foci of tubular necrosis
++	Extensive tubular necrosis
+++	Extensive tubular necrosis and focal necrosis of other tissues
++++	Large zone of necrosis of all tissue structures
ACUTE INFLAMMATORY RESPONSE	
0	No detectable inflammatory response
+	Minimal, focal infiltrates consisting of only a few polymorphonuclear neutrophils (PMN)
++	Multiple foci of PMN
+++	Patchy, moderate PMN infiltrate
++++	Dense extensive infiltrate of PMN

(Table 1).

Statistical analysis

Hemodynamic and blood sample data of the 60- and 90-minute ischemia groups were compared with each other and with their baseline values which served as control data. The degree of tissue damage and neutrophil infiltration was compared between the 60- and 90-minute ischemia groups. Analysis of variance with post-hoc Dunnett's test was used to determine the difference at each time point compared to baseline values. The six control animals were used to compare post-autopsy data. Comparison between the groups was made using paired Student's t-test with Bonferroni correction. Statistical significance was set at $p < 0.05$.

RESULTS

All animals underwent surgical preparation without preoperative complication. In particular there was no evidence of renal dysfunction during the recovery period. All animals survived for the duration of the experiment.

Table 2. Renal function during ischemia-reperfusion injury

Variable	Group	Baseline	Hours of reperfusion			
			4	8	16	24
Serum BUN	60	15.3 ± 1.3	21.1 ± 2.0	26.6 ± 2.3*	37.5 ± 4.0*	43.0 ± 5.4*
	90	14.5 ± 2.5	20.0 ± 2.0	26.0 ± 4.1*	37.5 ± 5.5*	50.0 ± 10.0*
Serum Cr	60	0.8 ± 0.1	1.5 ± 0.1	2.0 ± 0.2*	2.6 ± 0.3*	3.1 ± 0.5*
	90	1.0 ± 0.1	2.2 ± 0.4*	3.1 ± 0.1*	3.8 ± 0.2*	4.4 ± 0.1*
Urine output	60	3.6 ± 0.6	5.6 ± 2.8	3.7 ± 1.1	2.7 ± 1.3	3.0 ± 1.2
	90	2.4 ± 0.2	0.8 ± 0.6*	1.0 ± 0.4	1.4 ± 0.6	1.5 ± 0.7
CL	60	78.2 ± 4.2	13.7 ± 6.0*	20.7 ± 13.8*	19.6 ± 12.5*	13.7 ± 8.9*
	90	103.3 ± 10.5	6.7 ± 4.4*	5.9 ± 3.4*	3.5 ± 1.9*	3.6 ± 1.9

Values are mean ± standard deviation.

*: $p < 0.05$, compared with baseline value.

Blood urea nitrogen (BUN, mg%), Creatinine (Cr, mg%), Urine output (ml/kg/min), Creatinine clearance (CL, ml/min).

Induction of renal injury

Animals in both the 60- and 90-minute ischemic groups exhibited the typical features of acute renal failure, as evidenced by anuria during the ischemic period, progressive increase in serum creatinine and blood urea nitrogen concentration, as well as a decline in the creatinine clearance. During reperfusion, urine output showed wide variation between each animal (Table 2). Blinded renal histopathology confirmed that significant renal damage had occurred in both ischemic groups. Using the above-described rating scale, kidneys from the 60-minute ischemic group revealed a mild-to-moderate degree of tubular damage and minimal neutrophil infiltration (tissue injury scale; 1.8 ± 0.3 , inflammation scale; 0.4 ± 0.2). In the 90-minute ischemic group, renal histopathology revealed frank necrosis with karyolysis of most tubular segments within the cortex, and a moderately dense acute inflammatory infiltration, consisting mostly of neutrophils, was noted in the interstitial area of the outer cortex (tissue injury scale; 2.8 ± 0.4 , inflammation scale; 1.5 ± 0.3) (Fig. 1).

Hemodynamic alterations

Occlusion of the renal arteries resulted in a sig-

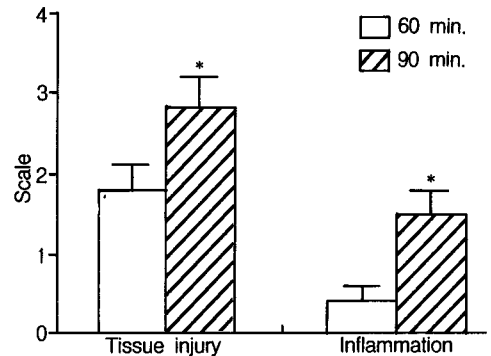


Fig. 1. Comparison of the degree of inflammation and tissue damage in kidneys between 60- and 90-minute renal ischemia-reperfusion groups (60 min. and 90 min., respectively). Scale means the degree of inflammation and tissue damage in kidneys, based on Table 1.

*: $P < 0.05$ between groups.

nificant, progressive increase in mean arterial pressure which resolved after 4 hours of reperfusion in both ischemic groups (Table 3). There was also a rise in mean pulmonary artery pressure in both ischemic groups during the reperfusion period. This rise in mean pulmonary artery pressure was statistically significant at 4 and 8 hours after reperfusion in the 60-minute ischemic group, compared to its baseline value (Table 3). But the heart rates, cardiac

Table 3. Hemodynamic data during ischemia-reperfusion injury

Variable	Group	Baseline	Ischemia	Hours of reperfusion						
				0.5	1	2	4	8	16	24
HR	60	92±45	92±2	94±3	90±3	91±4	96±5	98±8	90±7	82±5
	90	94±8	87±6	94±5	94±4	101±5	104±5	109±6	100±4	90±4
MAP	60	93±6	112±8	115±7	119±2*	119±8*	117±8*	109±9	107±8	109±2
	90	93±6	116±9	120±8*	124±9*	119±9*	115±8	111±7	100±5	100±6
PAP	60	16±1	18±2	19±4	19±2	19±2	21±2*	21±1*	20±1	20±1
	90	19±2	21±2	21±2	23±2	22±1	23±1	23±1	23±2	22±2
CVP	60	6±1	6±1	6±1	6±1	7±1	7±1	8±1	7±1	7±1
	90	7±1	7±2	8±1	8±1	8±1	8±1	8±2	9±1	8±1
CI	60	6.4±0.4	5.8±0.5	6.4±0.4	6.7±0.8	6.2±0.7	6.2±0.4	5.8±0.5	5.5±0.3	5.7±0.3
	90	6.8±0.6	5.6±0.7	6.0±0.7	6.1±0.7	6.3±0.7	6.5±0.6	6.0±0.4	5.8±0.4	6.0±0.3

Values are mean±standard deviation.

*: p<0.05, compared to baseline value.

Heart rate (HR, rates/minute), Mean arterial pressure (MAP, mmHg), Pulmonary arterial pressure (PAP, mmHg), Central venous pressure (CVP, mmHg), Cardiac index (CI, l/min/m²).

Table 4. Blood gas analysis during ischemia-reperfusion injury

Variable	Group	Baseline	Ischemia	Hours of reperfusion						
				0.5	1	2	4	8	16	24
pH	60	7.46±0.02	7.47±0.01	7.48±0.01	7.46±0.01	7.48±0.01	7.49±0.01	7.50±0.01	7.48±0.01	7.46±0.01
	90	7.46±0.02	7.45±0.02	7.45±0.01	7.45±0.01	7.44±0.01	7.47±0.01	7.49±0.01	7.50±0.02	7.48±0.01
PaCO ₂	60	40±2	39±1	40±1	43±2	42±2	42±1	41±1.6	42±1.4	44±1.5
	90	38±1	39±1	40±1	41±1	39±1	39±2	38±2.1	41±2.2	42±2.0
PaO ₂	60	111±4	121±4	121±6	121±6	119±5	115±6	109±3	104±1	98±3
	90	112±3	117±6	117±5	113±3	120±2	113±4	115±6	103±3	107±3
BE	60	5.9±0.7	7.0±0.6	7.4±0.5	8.2±0.6	9.2±0.6	8.9±1.2	10.3±1.2*	8.5±1.2	7.35±1.5
	90	4.8±1.1	4.6±1.2	5.2±1.1	5.3±1.1	6.4±1.2	7.8±1.5	7.7±1.9	9.9±1.5*	9.25±1.1*

Values are mean±standard deviation.

*: p<0.05, compared to baseline value.

PaCO₂ (mmHg), PaO₂ (mmHg), Base excess (BE, mEq/l).

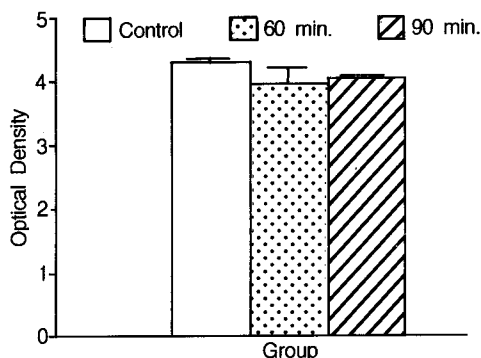


Fig. 2. Lung conjugated dienes were not significantly changed after 60- or 90-minute renal ischemia-reperfusion (60 min. and 90 min., respectively), compared to non-ischemic controls (control). Optical densities were measured at wave length 233 nm.

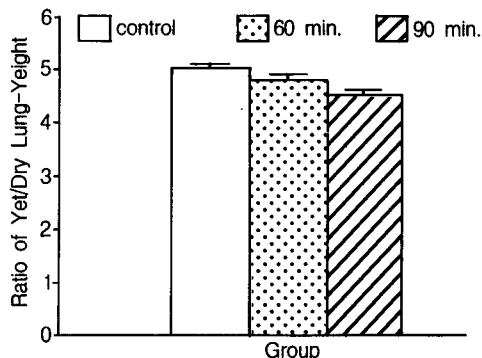


Fig. 3. Wet/dry lung-weight ratios were not significantly changed after 60- or 90-minute renal ischemia-reperfusion (60 min. and 90 min., respectively), compared to non-ischemic controls (control).

outputs, and central venous pressures during the ischemic and reperfusion periods were not significantly different between the two ischemic groups, and when compared to their baseline values (Table 3).

Blood gas alterations

In both the 60-minute and 90-minute ischemic groups, there were no significant changes in arterial or mixed venous pH, PO_2 , or PCO_2 (Table 4). Base excess increased in both ischemic groups during the reperfusion periods. However, this increase was significant only at 8 hours post-reperfusion in the 60-minute ischemic group and at 16 and 24 hours post-reperfusion in the 90-minute ischemic group (Table 4).

Conjugated dienes and wet/dry lung-weight ratio

Lung tissue conjugated dienes were not different when compared between the two ischemic groups (60 vs 90 minutes ischemia, 3.94 ± 0.25 vs 4.03 ± 0.04 O.D., respectively) or compared to non-ischemic controls (4.28 ± 0.06 O.D.) (Fig. 2).

Wet/dry lung-weight ratios were not significantly different when compared between the 60- and 90-minute ischemic groups (60 vs 90 minutes, 4.8 ± 0.1 vs 4.5 ± 0.1 , respectively) or compared to non-ischemic controls (5.0 ± 0.1) (Fig. 3).

DISCUSSION

Lower torso (Klausner *et al.* 1989d) and gut (Koike *et al.* 1994) ischemia-reperfusion injury has previously been shown to induce respiratory failure as evidenced by pulmonary hypertension, hypoxemia, and non-cardiogenic pulmonary edema. The mechanisms by which isolated organ ischemia-reperfusion injury induces dysfunction in the more distant lung are not clearly understood, although it is probable that neutrophil-endothelial interactions regulated by both humoral and local mediators are crucial. Oxygen-derived free radicals, proteases, cytokines, eicosanoids, complement activation products, and probably platelet activating factor and nitric oxide are involved as either signaling or effector molecules. These humoral and cellular mediators interact with the pulmonary vasculature and induce respiratory failure (Turnage *et al.* 1994). The most current, and popular, potential culprit in the pathogenesis of reperfusion injury is the oxygen-derived free radical (Fishbein, 1990). Despite its small size, the kidney receives 25% of the cardiac output. With this large blood supply, an ischemia-reperfusion injury may result in substantial oxygen free radical formation.

The formation of toxic oxygen metabolites is dependent on two important events which occur during

the ischemic period. These events prime the ischemic tissue for a reperfusion injury once adequate blood flow is restored. The first event is the accumulation of hypoxanthine as a result of the metabolic breakdown of adenosine triphosphate (ATP) (Galat *et al.* 1990). The second involves the proteolytic conversion of xanthine dehydrogenase to xanthine oxidase (Galat *et al.* 1990). The rate of this conversion is organ specific and shows species differences (Granger *et al.* 1986). For example, in the intestine the conversion is extremely rapid, requiring only one minute of ischemia to complete the conversion. This contrasts with the heart which requires 15 minutes of ischemia for the conversion and the kidney which requires more than one hour of ischemia before the conversion of xanthine dehydrogenase to xanthine oxidase. It has been suggested that there is species difference in renal tissue sensitivity to oxygen free radical injury (Southard *et al.* 1987). For example, following ischemia of the same degree, rat kidney shows a higher xanthine oxidase level and a higher ratio of xanthine oxidase to superoxide dismutase than dog or human kidneys. After these two ischemic events, accumulation of hypoxanthine and conversion to xanthine oxidase, the tissue is primed for reperfusion injury. Reintroduction of oxygen into this previously ischemic environment results in the rapid oxidation of hypoxanthine by xanthine oxidase with production of toxic oxygen metabolites (Galat *et al.* 1990). This important pathophysiologic mechanism is thought to contribute to renal disease including ischemia-reperfusion in a number of animal models (Klausner *et al.* 1988; Yoshioka and Ichikawa, 1989). However, the role of oxygen free radicals in ischemic renal injury remains controversial as several investigators do not agree that antioxidants confer protection, nor do all agree on the presence of increased lipid peroxidation or generation of oxygen free radicals in ischemia (Gamelin and Zager, 1988; Bonventre, 1993).

The neutrophils present in the post-ischemic tissue are thought to play a major role in the production of oxygen free radicals (Klausner *et al.* 1989a). Linas *et al.* suggested that neutrophils contribute to ischemia reperfusion injury by an O_2 metabolite mechanism in rat kidney (Linas *et al.* 1988). These neutrophils can directly participate in the damage to

epithelial or endothelial cells or they can act via production of inflammatory cytokines. In addition to the production of oxygen free radicals in response to ischemia-reperfusion injury, production of cytokines and arachidonic acid metabolites may also contribute to distant pulmonary dysfunction (Klausner *et al.* 1989d; Snyder *et al.* 1989). It has also been shown that neutropenia prevents the development of increased microvascular permeability after ischemia-reperfusion injury (Klausner *et al.* 1989a). However, the role of the neutrophil as a mediator of renal ischemia reperfusion injury was not settled. It has been also suggested that neutrophils and neutrophil adherence were not critical participants *in vivo* renal ischemia reperfusion injury (Thornton *et al.* 1989).

In the present experiment, we were able to establish renal damage in both the 60- and 90- minute ischemic groups as evidenced by the development of features typical of acute renal failure, elevated serum creatinine and blood urea nitrogen concentration, as well as a decline in creatinine clearance. The histopathologic findings also demonstrated the development of significant renal injuries. The histopathologic changes were more significant in the 90- minute ischemic group, as evidenced by frank necrosis and neutrophil infiltration. While the neutrophil may play a major role in the development of renal ischemia-reperfusion injury, the minimal accumulation of neutrophils in the 60-minute ischemic group is consistent with findings of other investigators. Thornton *et al.* also could not find prominent neutrophil infiltration in rabbit kidney tissue which was performed with 50-minute ischemia-reperfusion (Thornton *et al.* 1989). In a rabbit model of zymosan-activated plasma in combination with a short hypoxic period, which resulted in whole body inflammation, the kidneys showed only mild accumulation of neutrophils compared to the heart, liver, and spleen (Nuytinck *et al.* 1986). Nuytinck *et al.* in an autopsy study of shock and trauma patients, found significant generalized inflammation with increased organ weights in multiple organs, but could only demonstrate nephrotubulopathy without significant neutrophil infiltration into the kidney (Nuytinck *et al.* 1988).

One of the remote consequences of ischemia reperfusion is non-cardiogenic pulmonary edema, an early manifestation of the adult respiratory distress

syndrome. This is secondary to neutrophil-mediated abnormal permeability of the lung microvasculature to protein. It is assumed that the larger the mass of ischemic tissue and the longer the ischemic time, the more probable it is that remote lung injury will occur (Welbourn *et al.* 1991).

In our study, despite the apparent establishment of a renal ischemia-reperfusion model, there was no significant pulmonary dysfunction. There was a significant increase in pulmonary artery pressure in the 60-minute ischemic group, which may be caused by the activation of renin-angiotensin cascade after renal artery occlusion, but it could not be defined as pulmonary hypertension because of only minor increases. Also, there was no evidence of hypoxemia. Although the blood free wet/dry lung-weight ratio is a well established method of quantitating pulmonary edema, we could not demonstrate the development of pulmonary edema in either ischemic groups. In addition, we were unable to demonstrate the increased levels of conjugated dienes in lung tissue 24 hours after reestablishment of reperfusion.

Failure of isolated kidney ischemia-reperfusion injury to induce pulmonary dysfunction may be due to several factors. Firstly, as stated above, the conversion of xanthine dehydrogenase to xanthine oxidase in the kidney requires over one hour of ischemia, therefore it may be that a longer ischemic period would induce pulmonary dysfunction. Secondly, despite receiving a large percentage of cardiac output, the kidney may be too small as an organ to produce enough oxygen free radicals or preinflammatory materials for inducing remote organ injury. Thirdly, the decreased renal metabolic rate in the ischemic kidney, due to the decrease of renal blood flow and glomerular filtration rate, may be one factor in producing insufficient oxygen free radicals for inducing pulmonary dysfunction. Another possibility is that the damaged kidney does not accumulate neutrophils to the same degree as other damaged organs (for example, intestine and lower limbs) do. Thus, despite the important role of the neutrophil in the development of oxygen free radicals and other inflammatory mediators, the relative paucity of neutrophil accumulation in the kidney may be insufficient to induce distant organ dysfunction. Finally, there may be species differences in which the sheep kidney may react differently to

ischemia-reperfusion compared to that of other species.

Conclusively, bilateral kidney ischemia-reperfusion in sheep does not induce hypoxemia, pulmonary edema, pulmonary hypertension, and an increase of lung tissue conjugated dienes.

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