

Effect of saline infusion for the maintenance of blood volume on pulmonary gas exchange during temporary abdominal aortic occlusion

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Abstract

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We analyzed the effects of saline infusion for the maintenance of blood volume on pulmonary gas exchange in ischemia-reperfusion syndrome during temporary abdominal aortic occlusion in dogs. We studied 20 adult mongrel dogs weighing 12 to 23 kg divided into two groups: ischemia-reperfusion group (IRG, N = 10) and IRG submitted to saline infusion for the maintenance of mean pulmonary arterial wedge pressure between 10 and 20 mmHg (IRG-SS, N = 10). All animals were anesthetized and maintained on spontaneous ventilation. After obtaining baseline measurements, occlusion of the supraceliac aorta was performed by the inflation of a Fogarty catheter. After 60 min of ischemia, the balloon was deflated and the animals were observed for another 60 min of reperfusion. The measurements were made at 10 and 45 min of ischemia, and 5, 30, and 60 min of reperfusion. Pulmonary gas exchange was impaired in the IRG-SS group as demonstrated by the increase of the alveolar-arterial oxygen difference (21 ± 14 in IRG-SS vs 11 ± 8 in IRG after 60 min of reperfusion, $P = 0.004$ in IRG-SS in relation to baseline values) and the decrease of oxygen partial pressure in arterial blood (58 ± 15 in IRG-SS vs 76 ± 15 in IRG after 60 min of reperfusion, $P = 0.001$ in IRG-SS in relation to baseline values), which was correlated with the highest degree of pulmonary edema in morphometric analysis (0.16 ± 0.06 in IRG-SS vs 0.09 ± 0.04 in IRG, $P = 0.03$ between groups). There was also a smaller ventilatory compensation of metabolic acidosis after the reperfusion. We conclude that infusion of normal saline worsened the gas exchange induced by pulmonary reperfusion injury in this experimental model.

Key words

- Reperfusion lesion
- Fluid resuscitation
- Pulmonary gas exchange
- Lung edema

Introduction

Surgical procedures requiring aortic occlusion have been associated with ischemia-reperfusion lesions with homeostatic distur-

bances in virtually all organ systems in the body. Despite improvements in surgical and anesthetic management, complications are common, with high rates of morbidity and mortality (1-3).

After aortic declamping, severe hypotension with decreased cardiac output is a well-known occurrence secondary to the precipitous reduction in vascular resistance, sequestration of blood volume in the distal capillary beds, and the negative inotropic effect of acidosis and myocardial depressant factors. The potential for hypovolemia may be worsened by intravascular fluid loss caused by capillary damage with reperfusion (4-7).

The amount of resulting hypovolemia during declamping can be attenuated by volume expansion. Fluid administration followed by adequate monitoring based on the physiology of cardiac function promotes good myocardial performance during surgical stress and in the postoperative period. It improves cardiac output and maintains systemic blood pressure, which is important for adequate coronary blood flow, thereby protecting the heart especially in patients with coronary occlusive disease (4-12).

Maintenance of pulmonary artery wedge pressure between 10 and 18 mmHg during this procedure could prevent a decline in cardiac output and hypotension after aortic declamping (5-7,13-15). However, few studies have evaluated the impact of fluid infusion on pulmonary gas exchange. Furthermore, among the possible complications, the pulmonary ones have high incidence and mortality rate, which is mostly a consequence of pulmonary edema caused by ischemia and reperfusion of the aorta (16-22).

In view of the importance of the study of ischemia-reperfusion damage and of its potential in determining systemic alterations even in distant organs such as the lung, we conducted the present experiment. Our objective was to assess the effects of saline infusion for the maintenance of mean pulmonary artery wedge pressure between 10 and 20 mmHg during aortic ischemia-reperfusion on dogs, especially in the shock phase after aortic declamping, on pulmonary gas exchange.

Material and Methods

Male adult mongrel dogs weighing 12 to 23 kg (N = 20) were anesthetized intravenously with sodium thionembutal (Sodium Thiopental® CEME, Ministério da Saúde, Brasília, DF, Brazil - Brazil's Health Department) with an initial dose of 20 mg/kg, followed by 5 mg/kg as needed to maintain anesthesia during the procedure. After induction of anesthesia, the dogs underwent endotracheal intubation with an 8-mm cannula and were allowed to breathe room air without mechanical ventilation throughout the experiment.

The left femoral artery was dissected and catheterized with an 8 French Fogarty occluder, and the balloon was positioned in the descending thoracic aorta adjacent to the diaphragm at the level of the 10th thoracic vertebra for later occlusion. Aortic occlusion was therefore performed above the celiac trunk. Physical examination, laparotomy, and thoracotomy confirmed the correct position of the balloon at the end of the procedure in all dogs.

An 8 French polyethylene catheter was introduced through the right femoral artery, and its distal end was located in the distal abdominal aorta for monitoring mean abdominal aortic artery pressure distal to the occlusion. The mean systemic arterial pressure above the level of aortic occlusion was also monitored through the right carotid artery with an 8 French polyethylene catheter.

A triple-lumen model 7 French thermodilation pulmonary artery catheter was inserted through the right internal jugular vein and its progression was controlled by visualization of the pressure curves on an SDM2000 monitor (Dixtal Tecnologia, Manaus, AM, Brazil). The distal tip of the catheter was placed in the pulmonary artery. The proximal and distal portions of the pulmonary artery catheter were connected to a Statham P23 pressure transducer (Statham, Oxnard, CA, USA), permitting the determination of pressure

curves of the right atrium, pulmonary artery, and pulmonary arterial wedge. The last hemodynamic variable was estimated through the pulmonary artery occlusion pressure, obtained with the inflation of the balloon at the distal end of the catheter. Cardiac output was determined by the thermodilution technique (23) with the debitometer of an SDM 2000 monitor (Dixtal Tecnologia).

The dogs were randomly assigned to two groups: ischemia-reperfusion (IRG, N = 10) and ischemia-reperfusion with saline infusion (IRG-SS, N = 10). In both groups, the criteria for the beginning of the experiment were arterial blood pH ≥ 7.25 , arterial blood oxygen partial pressure ≥ 70 mmHg, mean pulmonary arterial wedge pressure ≥ 5 mmHg, and mean systemic arterial pressure ≥ 90 mmHg.

In the IRG, we first obtained baseline hemodynamic, metabolic and respiratory measurements (T0), and then performed aortic occlusion by inflating the Fogarty occluder with saline until mean systemic arterial pressure below the occlusion reached values between 10 and 20 mmHg and mercury column oscillation was not observed. After 60 min of aortic occlusion, the balloon was deflated and reperfusion was started. The animals were observed for another 60 min and then were sacrificed by venous administration of 50 mEq potassium chloride. Open thoracotomy was then performed and two fragments of the left cardiac lung lobe were removed for histopathologic and morphometric analysis. Hemodynamic, metabolic and respiratory measurements were repeated at 10 min of ischemia (T10-I), 45 min of ischemia (T45-I), 5 min of reperfusion (T5-R), 30 min of reperfusion (T30-R), and 60 min of reperfusion (T60-R). In the IRG-SS, the dogs underwent the same procedures and the same monitoring. The difference from the IRG group was the administration of saline solution in order to maintain mean pulmonary arterial wedge pressure between 10 and 20 mmHg throughout the experiment.

For the collection of expired gas, the endotracheal cannula was attached to a Douglas bag through a two-way valve (Hans Rudolph Inc., Kansas City, MO, USA). After mixing, a gas sample was analyzed with a gas analyzer (ABL 330, Radiometer, Copenhagen, Denmark).

The pulmonary parameters studied were: respiratory rate, expiratory minute volume (\dot{V}_E), partial pressure of oxygen in arterial blood (P_{aO_2}), hemoglobin oxygen saturation in arterial blood (SaO_2), partial pressure of carbonic gas in arterial blood (P_{aCO_2}), partial pressure of oxygen in alveolar gas (P_{AO_2}), alveolar-arterial oxygen gradient ($P(A-a)O_2$), alveolar dead space fraction (V_D/V_T), respiratory quotient, and partial pressure of oxygen in venous blood (P_{vO_2}). The hemodynamic parameters studied were: mean systemic arterial pressure, mean pulmonary arterial wedge pressure, and cardiac index. The metabolic parameters studied were: arterial pH, arterial bicarbonate (HCO_3^-), and lactate.

The V_D/V_T ratio was calculated by Enghoff modification of the Bohr equation (24): $V_D/V_T = (P_{aCO_2} - P_{E}CO_2) \div P_{aCO_2}$, where $P_{E}CO_2$ is the partial pressure of carbon dioxide in expired gas.

Morphometric analysis was carried out by the point-counting technique. For this purpose we used an optical microscope equipped with an integrating eyepiece containing 100 points and 50 lines. We studied the alveolar edema index. At a magnification of 400, we analyzed 10 randomly selected fields of the proximal section and 10 fields of the distal section. The correlation between the number of points of the eyepiece falling on alveolar edema and the number of points falling on the whole alveolar lumen was determined (25).

Differences between groups regarding hemodynamic, metabolic and pulmonary variables were studied by multivariate analysis of profiles with repeated measurements analyzing variations in relation to baseline

values and the parallelism and coincidence of parameters between groups (26). Differences in alveolar edema index between the two groups were analyzed with the Student *t*-test. The level of significance was set at 5% ($P < 0.05$) in all analyses.

The study was approved by the Ethics Committee for Animal Research of Escola Paulista de Medicina (Paulista Medical School), Universidade Federal de São Paulo (Federal University of São Paulo), São Paulo, SP, Brazil.

Results

Significant hemodynamic parameters are shown in Table 1. For the IRG-SS group, the values of mean pulmonary arterial wedge pressure during the whole procedure were within the range stipulated for this experimental model, i.e., 10 to 20 mmHg. Furthermore, saline infusion was suitable for minimizing hemodynamic changes, avoiding hypotension ($P = 0.04$ for parallelism between groups) and a decrease in the cardiac index ($P = 0.01$ for parallelism between groups) after aortic declamping.

Significant respiratory parameters are shown in Figure 1, Table 2, and Table 3. After aortic declamping, a decrease in base-

line values ($P = 0.001$ in T45-R and $P = 0.001$ in T60-R) occurred for PaO_2 in IRG-SS but not in IRG. The same pattern was observed regarding SaO_2 ($P = 0.047$ for parallelism between groups). P(A-a)O_2 was increased in IRG-SS after aortic declamping ($P = 0.014$ in T30-R and $P = 0.004$ in T60-R), but not in IRG. Although V_E increased in both groups, it was greater in IRG ($P = 0.039$ for coincidence between groups). PaCO_2 decreased in IRG but not in IRG-SS ($P = 0.007$ for coincidence between groups). V_D/V_T was increased in both groups after aortic occlusion. However, the increase was greater in IRG-SS ($P = 0.024$ for coincidence between groups). No difference was observed between groups regarding respiratory rate ($P = 0.510$ for parallelism and $P = 0.963$ for coincidence between groups) or respiratory quotient ($P = 0.561$ for parallelism and $P = 1.591$ for coincidence between groups).

Significant metabolic parameters and PvO_2 are shown in Table 4. Acidosis was greater in IRG-SS ($P = 0.046$ for coincidence between the groups). HCO_3^- always showed lower values in IRG-SS than in IRG ($P = 0.003$ for parallelism between the groups). Lactate was similar in both groups. No difference was observed between groups regarding $\text{P}\bar{\text{v}}\text{O}_2$.

Table 1. Effect of ischemia-reperfusion with saline infusion on mean pulmonary arterial wedge pressure (MPAWP), mean systemic arterial pressure (MAP) and cardiac index (CI) in the ischemia-reperfusion group (IRG) and the group submitted to ischemia-reperfusion with saline infusion (IRG-SS).

	MPAWP (mmHg)		MAP (mmHg)		CI ($\text{L min}^{-1} (\text{m}^2)^{-1}$)	
	IRG	IRG-SS	IRG	IRG-SS	IRG	IRG-SS
T0	7 ± 2	7 ± 3	133 ± 12	128 ± 17	5.70 ± 1.17	5.79 ± 2.72
T10-I	13 ± 8	19 ± 5*	174 ± 24*	176 ± 24*	4.96 ± 1.83	5.73 ± 1.69
T45-I	11 ± 4	18 ± 5*	175 ± 20*	161 ± 28*	4.26 ± 1.31*	4.07 ± 1.12*
T5-R	3 ± 2	13 ± 5*	97 ± 27*	120 ± 23	2.72 ± 0.69*	5.25 ± 0.92
T30-R	2 ± 1*	12 ± 2*	101 ± 14*	124 ± 20	2.65 ± 0.81*	5.47 ± 1.54
T60-R	2 ± 1*	10 ± 2*	94 ± 14*	117 ± 18	2.47 ± 0.63*	5.28 ± 1.42

Data are reported as means ± SD. Measurements were made at 0 (T0), 10 (T10-I) and 45 (T45-I) min of ischemia (I) and at 5 (T5-R), 30 (T30-R) and 60 (T60-R) min of reperfusion (R).

There was a difference in parallelism between IRG and IRG-SS for each parameter measured ($P < 0.05$, repeated-measures analysis of variance). * $P < 0.05$ compared to baseline values (repeated-measures analysis of variance).

Histopathologic and morphometric analysis demonstrated pulmonary edema and congestion, mainly interstitial, in both groups. The alveolar edema index was more intense in IRG-SS (0.16 ± 0.06 vs 0.09 ± 0.04 ; $P = 0.030$).

Discussion

As demonstrated in several studies, saline infusion with maintenance of mean pulmonary arterial wedge pressure is suitable for minimizing hemodynamic changes after release of the aortic clamps, mainly avoid-

ing hypotension and a decrease in cardiac index (5-7,13-15). However, in the present study this procedure caused worsening of gas exchange as shown by an increase in $P(A-a)O_2$ after aortic declamping in IRG-SS, determining a progressive decrease in PaO_2 . SaO_2 also had decreased progressively due to hypoxemia and to the reduction of the affinity of hemoglobin for oxygen due to the greater acidosis in IRG-SS.

Morphometric analysis demonstrated more intense pulmonary edema in IRG-SS, determining a decrease in gas exchange in individuals of this group.

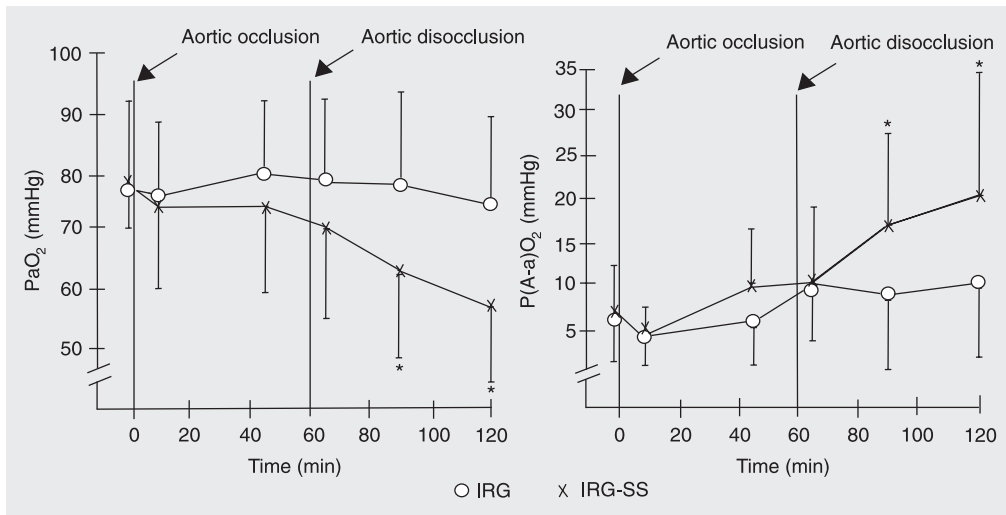


Figure 1. Changes in arterial blood partial oxygen pressure (PaO_2) and alveolar-arterial oxygen gradient ($P(A-a)O_2$) in the ischemia-reperfusion group (IRG, circles) and the group submitted to ischemia-reperfusion with saline infusion (IRG-SS, crosses). * $P < 0.05$ vs IRG (repeated-measures analysis of variance).

Table 2. Effect of ischemia-reperfusion with saline infusion on respiratory rate (f), expiratory minute volume (V_E), alveolar-arterial oxygen gradient ($P(A-a)O_2$), and alveolar dead space fraction (V_D/V_T) in the ischemia-reperfusion group (IRG) and the group submitted to ischemia-reperfusion with saline infusion (IRG-SS).

	f (bpm)		V_E (L/kg)		$P(A-a)O_2$ (mmHg)		V_D/V_T	
	IRG	IRG-SS	IRG	IRG-SS	IRG	IRG-SS	IRG	IRG-SS
T0	25±12	26±16	0.30±0.12	0.34±0.12	6±5	7±5	0.52±0.17	0.55±0.10
T10-I	59±18*	53±27*	0.37±0.11*	0.45±0.11*	4±3	4±3	0.62±0.11*	0.73±0.11*
T45-I	47±16*	45±18	0.41±0.10*	0.41±0.11*	6±5	10±7	0.58±0.13	0.71±0.11*
T5-R	56±10*	63±22*	0.57±0.23*	0.63±0.19*	10±6	11±8	0.63±0.10*	0.73±0.06*
T30-R	57±14*	60±28*	0.56±0.23*	0.47±0.14	9±8	17±11	0.59±0.13	0.73±0.08*
T60-R	48±9*	56±26	0.51±0.20*	0.48±0.15*	11±8	21±14*	0.65±0.12	0.72±0.09*

Data are reported as means ± SD. Measurements were made at 0 (T0), 10 (T10-I) and 45 (T45-I) min of ischemia (I) and at 5 (T5-R), 30 (T30-R) and 60 (T60-R) min of reperfusion (R).

There was a difference in coincidence between IRG and IRG-SS for V_E and V_D/V_T ($P < 0.05$, repeated-measures analysis of variance). * $P < 0.05$ compared to baseline values (repeated-measures analysis of variance).

Moreover, mean pulmonary arterial wedge pressure always remained below 18 mmHg during the reperfusion period in IRG-SS and the cardiac index also increased, demonstrating the non-cardiogenic etiology of the pulmonary edema.

Other investigators have provoked pulmonary edema to a greater or lesser extent in different models of ischemia-reperfusion

injury. Anner et al. (27) detected areas of alveolar edema in dogs submitted to ischemia for aortic cross-clamping for 4 h followed by 4 h of reperfusion, Klausner et al. (28), using a sheep model of ischemic-reperfusion injury for 2 h of bilateral hind limb tourniquet ischemia, followed by 4 h of reperfusion, detected pulmonary edema by histopathological analysis, and Nielsen et al.

Table 3. Effect of ischemia-reperfusion with saline infusion on partial oxygen pressure in arterial blood (PaO₂), partial carbonic gas pressure in arterial blood (PaCO₂), hemoglobin oxygen saturation in arterial blood (SaO₂), and respiratory quotient in the ischemia-reperfusion group (IRG) and the group submitted to ischemia-reperfusion with saline infusion (IRG-SS).

	PaO ₂ (mmHg)		PaCO ₂ (mmHg)		SaO ₂ (%)		Respiratory quotient	
	IRG	IRG-SS	IRG	IRG-SS	IRG	IRG-SS	IRG	IRG-SS
T0	79±13	80±8	41±8	40±6	95±1	94±1	0.7±0.3	0.8±0.1
T10-I	77±13	74±14	44±5	46±4*	89±7	89±7*	0.7±0.3	0.8±0.1
T45-I	81±11	74±14	34±6*	42±4	94±3	90±6*	0.6±0.2	0.8±0.1
T5-R	80±14	70±15	34±6*	43±7	90±5	80±19*	0.8±0.2	0.8±0.1
T30-R	79±15	63±15*	33±6	44±13	93±2	86±9*	0.6±0.2	0.7±0.1
T60-R	76±15	58±15*	33±7	44±13	93±3	76±17*	0.6±0.2	0.6±0.1

Data are reported as means ± SD. Measurements were made at 0 (T0), 10 (T10-I) and 45 (T45-I) min of ischemia (I) and at 5 (T5-R), 30 (T30-R) and 60 (T60-R) min of reperfusion (R).

There was a difference in parallelism between IRG and IRG-SS for SaO₂ (P < 0.05, repeated-measures analysis of variance). There was a difference in coincidence between IRG and IRG-SS for PaCO₂ (P < 0.05, repeated-measures analysis of variance). *P < 0.05 compared to baseline values (repeated-measures analysis of variance).

Table 4. Effect of ischemia-reperfusion with saline infusion on arterial blood pH (pHa), arterial blood bicarbonate (HCO₃⁻), partial oxygen pressure in venous blood (PvO₂), and lactate in the ischemia-reperfusion group (IRG) and the group submitted to ischemia-reperfusion with saline infusion (IRG-SS).

	pHa		HCO ₃ ⁻ (mEq/L)		PvO ₂ (mmHg)		Lactate (mg/100 mL)	
	IRG	IRG-SS	IRG	IRG-SS	IRG	IRG-SS	IRG	IRG-SS
T0	7.28±0.08	7.31±0.07	18.5±2.9	19.1±3.4	58±15	47±6	13±4	12±6
T10-I	7.22±0.11	7.13±0.07*	16.9±2.7*	14.5±2.0*	54±4	56±5	-	-
T45-I	7.20±0.10*	7.08±0.08*	12.8±2.5*	12.1±1.7*	62±4*	59±4*	35±10*	36±18*
T5-R	7.11±0.11*	7.01±0.10*	10.6±2.8*	10.3±1.6*	48±3	50±7	46±16*	48±21*
T30-R	7.15±0.13*	7.03±0.14*	11.4±2.7*	10.5±1.7*	51±13	46±6	-	-
T60-R	7.17±0.14	7.03±0.16*	11.8±3.0*	10.7±2.0*	52±14	39±10	28±15*	22±13*

Data are reported as means ± SD. Measurements were made at 0 (T0), 10 (T10-I) and 45 (T45-I) min of ischemia (I) and at 5 (T5-R), 30 (T30-R) and 60 (T60-R) min of reperfusion (R).

There was a difference in parallelism between IRG and IRG-SS for HCO₃⁻ (P < 0.05, repeated-measures analysis of variance). There was a difference in coincidence between IRG and IRG-SS for pHa (P < 0.05, repeated-measures analysis of variance). *P < 0.05 compared to baseline values (repeated-measures analysis of variance).

(29) also found pulmonary edema detected by the increase of the relation between the dry and humid weights of the lung in an experimental study with aortic cross-clamping with Fogarty occluder for 40 min followed by 2 h of reperfusion. Furthermore, increased micro-vascular permeability, edema and neutrophil infiltration of the lungs were reported in several studies on ischemic-reperfusion injury (18,19,27,30).

Although the mechanism of the ischemia-reperfusion lung injury is still unclear, a number of putative etiological factors, including oxidative stress (reactive oxygen species, ROS) (27,31-33), tumor necrosis factor (34), up-regulation of molecules on the surface of the cell membrane (P-selectin and E-selectin) (35), and neutrophil adherence receptors (CD18), have been proposed (36). Among the mediators, ROS play a prominent role in ischemic-reperfusion injury. ROS such as superoxide anion ($\cdot\text{O}_2$), hydrogen peroxide, hypochlorous acid, nitric oxide-derived peroxynitrite, and hydroxyl radical ($\cdot\text{OH}$) are produced within minutes of reperfusion and continue to be generated for hours after the restoration of blood flow to ischemic tissue, and damage cells directly by altering membrane proteins and phospholipids. Because these membrane constituents play crucial roles as receptors, enzymes, and ion channels, ROS can lead to fatal metabolic and structural derangements (22,32). The role for ROS as a source of significant reperfusion damage is further supported by studies showing that the potent antioxidant N-acetylcysteine administered before reperfusion ameliorate the ischemic-reperfusion injury (33).

The more intense pulmonary edema in IRG-SS agreed with findings of increased pulmonary microvascular permeability after ischemia and reperfusion of the aorta. Paterson et al. (37) and Grindlinger et al. (8) detected pulmonary edema without evidence of left ventricular failure in patients undergoing abdominal aortic aneurysm surgery.

In these studies, a mild increase in postoperative pulmonary arterial wedge pressure from 9 to 12 mmHg related to the large fluid infusion tended to promote a movement of fluid into the alveoli secondary to increased permeability.

Abnormalities of pulmonary blood flow and injury to the microcirculation are characteristic features of acute lung injury. Classically, right-to-left intrapulmonary shunt leading to arterial hypoxemia has been considered the primary physiological abnormality in the early acute lung injury that we observed here by a worsening of PaO_2 and P(A-a)O_2 in IRG-SS. However, the V_D/V_T ratio is markedly elevated very early in the course of non-cardiogenic pulmonary edema, an event that we also observed in IRG-SS (38,39). Possible mechanisms include injury of pulmonary capillaries by thrombotic and inflammatory mechanisms, obstruction of pulmonary blood flow in the extra-alveolar pulmonary circulation, and areas with a high ventilation-perfusion ratio as a result of the compromised pulmonary blood flow to lung regions that remain well ventilated. Regardless of the mechanism, it is clear that both altered excretion of carbon dioxide and impaired oxygenation are characteristic physiological abnormalities of the early phase of acute lung injury. Interestingly, an elevated V_D/V_T has been shown to be a predictor of mortality in non-cardiogenic pulmonary edema (39).

Furthermore, V_E was reduced in the IRG-SS, and became even worse with the increase of V_D/V_T . Consequently, PaCO_2 did not decrease in the IRG-SS during reperfusion. In fact, respiratory acidosis was associated with metabolic acidosis in the IRG-SS, as shown by the levels of PaCO_2 . The reduced V_E and the lack of respiratory compensation of metabolic acidosis reflect acute respiratory failure with fatigue of the respiratory muscles (40).

We conclude that, in the present experimental model, saline infusion for the main-

tenance of blood volume resulted in the worsening of pulmonary reperfusion injury and lung gas exchange, as observed by the increase of P(A-a)O₂, the decrease of PaO₂, impairment of the ventilatory compensation of metabolic acidosis after reperfusion, and increased alveolar edema index.

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