Pulmonary Gas Exchange Abnormalities Following Intravascular Coagulation

Reticuloendothelial Involvement

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The influence of reticuloendothelial (RE) blockade on the pulmonary hemodynamic and gas exchange response to thrombin induced low-grade intravascular coagulation was studied in dogs during fibrinolytic inhibition. Neither saline infusion nor experimentally induced RE blockade significantly increased pulmonary vascular resistance, physiologic dead space, or pulmonary venous admixture. Intravascular coagulation in the absence of RE blockade resulted in a significant ($p < 0.05$) elevation in pulmonary vascular resistance which was transient and returned to prechallenge levels over a two to four hour period. This response was not associated with any significant change in physiological dead space. In contrast, intravascular coagulation in the presence of RE blockade resulted in significant ($p < 0.05$) hemodynamic and gas exchange abnormalities. These included an acute elevation in pulmonary vascular resistance, a decrease in arterial oxygenation, an increase in pulmonary venous admixture, and a sustained elevation in physiologic dead space. These events were associated with an elevation in the lung wet-to-dry weight ratios. Gas exchange and hemodynamic alterations after thrombin infusion during RE blockade suggest a functional role for the reticuloendothelial system in the prevention of pulmonary injury during intravascular coagulation. Thus, this study suggests a possible role of the RES in minimizing pulmonary injury during states of increased microaggregate formation.

PREVIOUS STUDIES HAVE DOCUMENTED an important physiologic role for the reticuloendothelial system in both nonspecific and specific host defense.[9,14,20,23] Although the RES is composed of a diffuse collection of mobile and fixed mononuclear phagocytes, a major component of the RE system consists of the fixed phagocytic cells in the liver, spleen and bone marrow which mediate the rapid removal of blood-borne particulate matter.[20] In this regard the RES plays a central role in the vascular clearance of fibrin aggregates,[13] fibrin degradation products,[10] fibrin–fibrinogen complexes, and injured and disintegrated platelets.[12] Additionally, the RE system appears to regulate intravascular hemostasis through its clearance of blood thromboplastin and active thrombin.[10]

Previous studies have documented that RES clearance of a large class of autologous or test particulates is facilitated by a circulating opsonic α_2SB glycoprotein (plasma fibronectin; cold insoluble globulin).[2,19,20] Depletion of circulating opsonic protein results in a depression in RES clearance of test particles, and restoration of opsonin levels during the later post-blockade period is associated with a restoration of RE activity.[3,19,20] Trauma, burn and major surgery in both animals and man induces a reticuloendothelial failure which is correlated with opsonin depletion as detected by both bioassay and immunoassay.[2,22,24,26]

During RES phagocytic depression, intravascular challenge with test particulates results in a depressed hepatic uptake and an increased localization of test particles within the pulmonary vascular bed.[11,19,20,21] The observed inverse relationship between liver phagocytic clearance capacity and the degree of lung localization of blood-borne particulate matter led us to hypothesize that the RES may serve to protect the lung from injury induced by microembolization in states of accelerated intravascular coagulation. This relationship may be of great significance during septicemia following surgery, burn injury or trauma,

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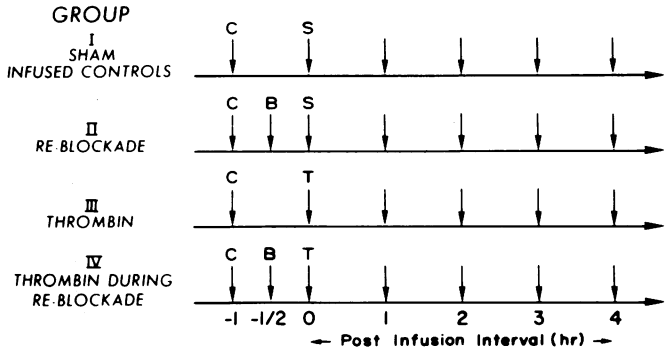

FIG. 1. Experimental design to test the effect of reticuloendothelial phagocytic blockade on the pulmonary consequences of thrombin-induced low-grade intravascular coagulation. Gas exchange and hemodynamic measurements were repeated at one, two, three and four hours after thrombin (T) or sham saline (S) challenge. RES blockade (B) was begun 30 minutes after control measurements (C) in groups II and IV.

where accelerated intravascular coagulation coexists with a depression in RE phagocytic capacity. In such states, lung microembolization may be augmented by the failure of the RES to clear circulating microthrombi, thus predisposing the lung to the development of interstitial or alveolar edema, ventilation perfusion abnormality, and associated gas exchange defects.

The present study was designed to test the hypothesis[20] that RE phagocytic depression would augment the degree of pulmonary insufficiency induced by low-grade intravascular coagulation, in terms of its effects on pulmonary vascular resistance, venous admixture and extravascular lung water.

Methods

For this study, 15 healthy mongrel dogs weighing 18–20 kg were used. They were anesthetized with sodium pentobarbital (30 mg/kg) iv and ventilated (Harvard Apparatus, Millis, MA) to maintain initial arterial P_{CO_2} values near 30 mmHg. Lungs were periodically hyperinflated to minimize atelectasis. The left femoral artery and vein were cannulated (polyethylene catheter) and a Swan-Ganz balloon-tipped catheter (Edwards Laboratories, Santa Ana, CA) was advanced from the right femoral vein into a pulmonary artery. Placement of the catheter tip was determined by pressure recordings and verified at autopsy. Intravascular pressures were measured using strain gauge pressure transducers zeroed at the right atrial reference level and recorded on a strip chart recorder. Pulmonary blood flow was measured with a densitometer (Gifford Instrument Laboratories, Oberlin, OH) using indocyanine green. Arterial and mixed venous P_{O_2}, P_{CO_2} and pH were measured with a blood gas analyzer (Radiometer, Copenhagen, Denmark), while mixed expired CO_2 was measured with an infrared CO_2 analyzer (Beckman Instruments, Schiller Park, IL).

Low-grade intrascular coagulation was induced by infusion of 155 Units/kg bovine thrombin (Parke-Davis, Detroit, MI) dissolved in a 3 ml/kg volume of 0.9% saline. The thrombin solution was divided into two equal volumes and each fraction was given simultaneously into both the descending aorta as well as the inferior vena cava over a 20 minute period. This protocol was selected to induce hemostasis and microaggregate formation on both the arterial and venous sides of the circulation at a level consistent with mild intravascular coagulation. The fibrinolytic blocker, trans-4-amino methyl-cyclohexanecarboxylic acid, (Abbott Laboratories) was administered to all animals 60 minutes prior to thrombin or sham infusion as a loading dose of 25 mg/kg. An additional 25 mg/kg was administered over the course of the four hour experiment as a slow intravenous infusion in order to maintain suppression of fibrinolytic activity.

Reticuloendothelial blockade was induced by intravenous injection of a 500 mg/kg dose of the gelatinized "RE-test-lipid emulsion"[5,19] prepared as an anhydrous base with glycerol, triolein, and soya lecithin in a ratio of 10:10:1 by weight, respectively.[5] The anhydrous base was diluted with 0.3% gelatin (Nutritional Biochemical Corp.) supplemented sterile 5% dextrose and water at a pH of 7.4 to yield a stable emulsion with a 20% anhydrous base concentration. The emulsion was incubated at 37 C for 30 minutes prior to its injection in order to affect gelatinization coating of the test particles.[19,21] As previously reported, this dose of emulsion produces an approximate 80% fall in serum opsonic activity in dogs within 15 minutes after intravenous injection, resulting in a selective RES depression for several hours.[5] The selective localization of this test colloid in the RES, especially the Kupffer cells, has been verified by electromicroscopy.[28]

Studies were conducted in four experimental groups (Fig. 1). These four groups were as follows:

Group I: Control—Fibrinolytic blocker with sham saline challenge (n = 3).
Group II: Control—Fibrinolytic blocker with RE blockade and sham saline challenge (n = 4).
Group III: Experimental—Fibrinolytic blocker with thrombin challenge (n = 4).
Group IV: Experimental—Fibrinolytic blocker with both RE blockade and thrombin challenge (n = 4).

Measurements of pulmonary hemodynamics and gas exchange were made 60 minutes prior to thrombin challenge, and were repeated at one, two, three, and four hours during the experimental period. Physiologic dead space was calculated using the Enghoff modifica-

tion of the Bohr equation[7] to obtain an index of the ventilation delivered to poorly perfused and nonperfused regions of the lung. Oxygen saturations were calculated from partial pressures with a Severinghaus blood-gas calculator.[27] A standard P_{50} of 28.2 was assumed to remain constant throughout the experimental period, since 2,3-Diphosphoglycerate levels were not measured. Pulmonary venous admixture was calculated using the oxygen mixing equation of Berggrens[1] while the animals were ventilated with room air. End-capillary oxygen saturations were calculated at the ideal alveolar P_{O_2} level using the pH and P_{CO_2} of arterial blood. At inspired oxygen fractions below 1.0, this technique provides an index of perfusion to nonventilated as well as poorly ventilated regions of the lung. Thus, during room air breathing this procedure ascribes the entire alveolar–arterial oxygen difference to an effective venous admixture.

At the conclusion of the study the lungs were removed, blotted dry and weighed. Lungs were then reinflated to approximately 30 cm H_2O airway pressure and air dried to a constant weight. Wet-to-dry weight ratios were then calculated to provide an index of extravascular lung water. Without a correction for residual blood volume in the lung, this technique assumes that residual blood volumes were not different among the four experimental groups.

Mean values are presented as ±1 SEM. Statistical significance was determined using the t-test, and statistical significance was determined at the 0.05 level of probability.

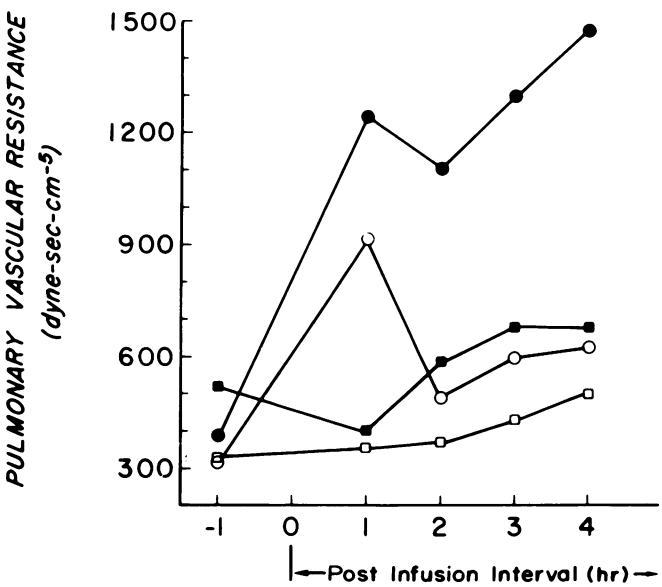

FIG. 2. Changes in mean pulmonary vascular resistance (PVR) produced by thrombin infusion with and without associated RES blockade. Following infusion at t = 0, PVR rose significantly in both groups given thrombin ($p < 0.05$). Thereafter, only the group given thrombin during RE blockade remained significantly elevated when compared to control levels. □: Sham infused controls. ■: RE blockade. ○: Thrombin. ●: Thrombin during RE blockade.

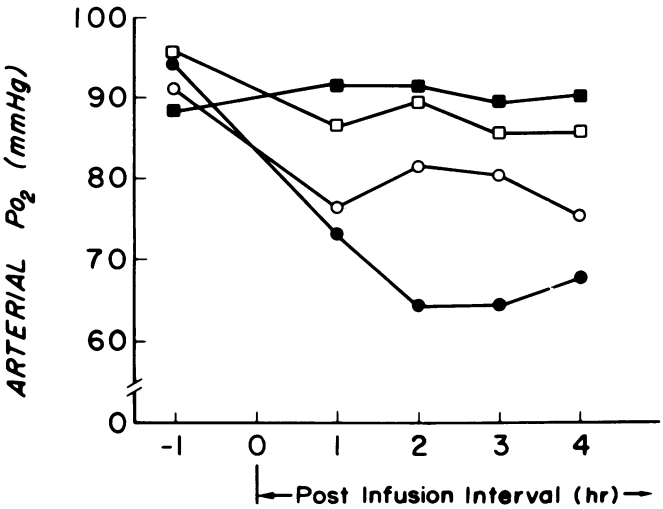

FIG. 3. Arterial oxygen tension as influenced by thrombin infusion with and without associated RE blockade. While P_{O_2} fell significantly in both groups challenged with thrombin, this decline was significantly greater in the RES blockaded group at two and three hours after challenge ($p < 0.05$). □: Sham infused controls. ■: RE blockade. ○: Thrombin. ●: Thrombin during RE blockade.

Results

Presented in Figure 2 is the pulmonary vascular resistance (PVR) observed after thrombin challenge alone or thrombin challenge in the presence of RE blockade. Animals challenged with thrombin or with thrombin during RE blockade demonstrated a significant ($p < 0.05$) elevation in pulmonary vascular resistance when compared to their respective prechallenged levels. In contrast, the PVR in non-RE blockaded thrombin infused animals demonstrated a progressive return toward control levels after an initial elevation. The rise in PVR was significantly ($p < 0.05$) greater for the animals subjected to thrombin during RE blockade than for any of the other groups at two, three, and four hours. Thus, thrombin challenge, and/or thrombin challenge during RE blockade both resulted in an acute elevation in the pulmonary vascular resistance, but this hemodynamic response was prolonged and maintained in the RE blockaded animals, whereas it was transient in the absence of prior RE depression.

Presented in Figure 3 is the arterial P_{O_2} of the four groups of animals over the four-hour experimental period. When compared to their respective prechallenged arterial P_{O_2} levels, the RE blockaded dogs challenged with thrombin demonstrated the greatest decline in arterial oxygenation. This decrease was apparent by one-hour postthrombin challenge and maintained over

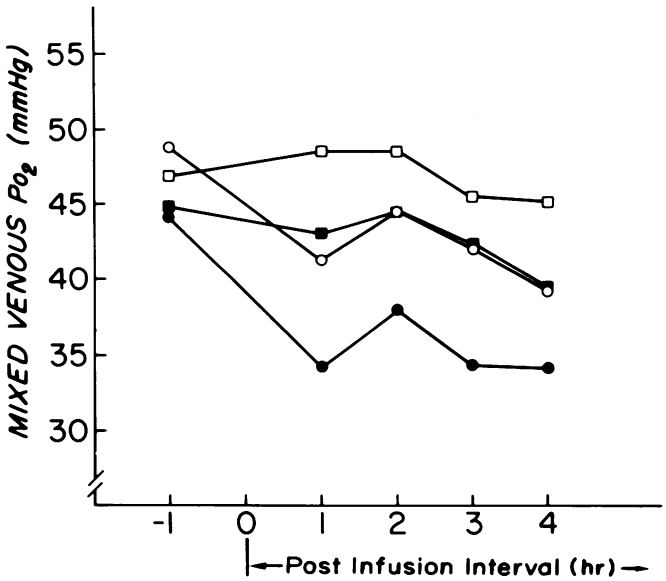

FIG. 4. Mixed venous oxygen tension as influenced by thrombin infusion with and without associated RES blockade. A significant and roughly parallel decline from prechallenge levels was seen in both groups challenged with thrombin. □: Sham infused controls. ■: RE blockade. ○: Thrombin. ●: Thrombin during RE blockade.

the four-hour experimental period. However, neither RE blockade nor saline infusion alone initiated these changes.

Mixed venous blood gas measurements were made in order to clarify the interpretation of the arterial blood gas values (Tables 1–4). In contrast to the saline infused control groups, both the animals challenged with thrombin and those challenged with thrombin during RE blockade underwent a significant and roughly parallel decline in mixed venous P_{O_2} during the study ($p < 0.05$) (Fig. 4).

The arterial and mixed venous blood gas data are reflected in the calculations of venous mixture. The venous admixture calculation at an inspired oxygen fraction of 0.209 provides an index of perfusion to nonventilated as well as poorly ventilated lung regions. In contrast to the groups subjected to RE blockade alone or thrombin infusion alone, there was a significant elevation in venous admixture in the group given thrombin during RE blockade (Fig. 5). This elevation was evident within one hour after infusion and remained significantly higher than any other group at two and three hours after challenge ($p < 0.05$).

Since microembolization might be expected to restrict or abolish perfusion in ventilated lung regions, physiologic dead space was assessed to evaluate these changes. Neither the sham infused control group nor the animals subjected to RE blockade alone exhibited any significant increase in physiologic dead space ($p > 0.05$) (Fig. 6). However, sham infused control dogs did undergo an unexplained 40% reduction in dead space ventilation that was not seen in any other group during the study. Those dogs given thrombin in the absence of RE blockade exhibited no significant change in dead space during the experimental period. These observations were in marked contrast to the physiologic dead space (V_D/V_T) observed in the animals challenged with thrombin during RES phagocytic blockade. Dead space rose progressively throughout the experimental period to reach a maximum of 0.38 over the three to four-hour period which was significantly ($p < 0.05$) higher than the preinfusion control value of 0.24.

Pulmonary blood flow was measured as a part of the evaluation of pulmonary hemodynamics. While pulmonary blood flow showed a tendency to decline over the four-hour period in all four of the experimental groups, this depression was not significantly different from control values ($p > 0.05$) except in the saline infused group at three and four hours after challenge ($p < 0.05$) (Tables 1–4). The possibility that cardiac output may have undergone a transient decline in the thrombin infused groups prior to the 1 hour measurements cannot be ruled out. Tables 1–4 provide specifics with regards to the measured parameters.

TABLE 1. *Pulmonary Gas Exchange in Dogs Subjected to Saline Challenge During Fibrinolytic Blockade**

Parameters†	Control	1 Hour Post-saline	2 Hours Post-saline	3 Hours Post-saline	4 Hours Post-saline
Pa_{O_2}‡	95.5 ± 3.8	86.8 ± 4.4	89.4 ± 1.7	85.6 ± 6.8	85.7 ± 3.0
Pv_{O_2}§	46.8 ± 3.2	48.5 ± 1.4	48.7 ± 1.2	45.5 ± 1.3	45.2 ± 2.4
Pa_{CO_2}‖	30.3 ± 1.3	26.5 ± 1.7	25.8 ± 0.6	26.6 ± 0.2	28.4 ± 1.6
pH¶	7.42 ± 0.01	7.39 ± 0.01	7.38 ± 0.02	7.37 ± 0.03	7.35 ± 0.05
Ca_{O_2}#	16.75 ± 0.50	16.43 ± 0.44	16.53 ± 0.37	16.25 ± 0.24	16.22 ± 0.15
Cv_{O_2}**	12.41 ± 0.66	12.45 ± 0.36	12.59 ± 0.21	11.96 ± 0.35	11.61 ± 0.32
Cc'_{O_2}‡‡	17.06 ± 0.45	17.08 ± 0.45	17.07 ± 0.43	17.06 ± 0.41	17.00 ± 0.34
$\dot{Q}_s/\dot{Q}_t$§§	6.9 ± 1.8	14.5 ± 3.1	12.2 ± 1.4	15.2 ± 4.5	14.1 ± 3.8
$\dot{Q}_t$‖‖	2.5 ± 0.3	2.4 ± 0.2	2.3 ± 0.1	2.0 ± 0.1	2.0 ± 0.1

* Values are expressed as mean ± 1 SEM (n = 3).

† Key to symbols: ‡ Arterial oxygen tension (mmHg). § Mixed venous oxygen tension (mmHg). ‖ Arterial CO_2 tension (mmHg). ¶ Arterial pH. # Arterial oxygen content (volumes per cent). ** Mixed venous oxygen content (volumes per cent). ‡‡ Alveolar end capillary oxygen content (volumes per cent). §§ Pulmonary venous admixture (per cent). ‖‖ Cardiac output (L/min).

TABLE 2. *Pulmonary Gas Exchange in Dogs Subjected to RES Phagocytic Blockade During Fibrinolytic Blockade**

Parameters†	Control	1 Hour Post-RES Blockade	2 Hours Post-RES Blockade	3 Hours Post-RES Blockade	4 Hours Post-RES Blockade
Pa_{O_2}‡	88.6 ± 5.5	91.5 ± 9.3	91.2 ± 7.6	89.3 ± 6.7	90.1 ± 6.7
Pv_{O_2}§	44.9 ± 1.9	43.2 ± 3.3	44.6 ± 1.9	42.3 ± 1.1	39.6 ± 2.2
Pa_{CO_2}‖	26.8 ± 1.4	24.5 ± 1.9	24.7 ± 0.9	27.9 ± 1.1	24.3 ± 0.6
pH¶	7.43 ± 0.03	7.41 ± 0.03	7.41 ± 0.03	7.40 ± 0.03	7.40 ± 0.03
Ca_{O_2}#	19.3 ± 0.7	19.2 ± 0.5	19.3 ± 0.6	19.3 ± 0.7	19.3 ± 0.6
Cv_{O_2}**	14.3 ± 0.3	13.9 ± 0.5	14.2 ± 0.3	13.5 ± 0.5	13.0 ± 0.8
Cc'_{O_2}‡‡	19.9 ± 0.8	19.9 ± 0.8	20.0 ± 0.8	20.0 ± 0.8	20.0 ± 0.8
$\dot{Q}_s/\dot{Q}_t$§§	9.7 ± 2.7	9.4 ± 3.3	10.1 ± 3.1	9.6 ± 2.7	10.2 ± 3.2
$\dot{Q}_t$‖‖	2.1 ± 0.4	2.1 ± 0.2	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1

* Values are expressed as mean ± 1 SEM (n = 4).

† Key to symbols: ‡ Arterial oxygen tension (mmHg). § Mixed venous oxygen tension (mmHg). ‖ Arterial CO_2 tension (mmHg). ¶ Arterial pH. # Arterial oxygen content (volumes per cent). ** Mixed venous oxygen content (volumes per cent). ‡‡ Alveolar end capillary oxygen content (volumes per cent). §§ Pulmonary venous admixture (per cent). ‖‖ Cardiac output (L/min).

As an index of lung water accumulation, lung wet-to-dry weight ratios were evaluated. Figure 7 depicts the wet-to-dry weight ratios in the four experimental groups. Thrombin administration induced a significant increase in lung wet-to-dry weight ratios when compared to the sham infused control or RE blockade groups ($p < 0.05$). In contrast to thrombin challenge in the absence of RE blockade, it was apparent that the presence of RE depression during experimentally produced intravascular coagulation led to a significant elevation in lung wet-to-dry weight ratio to an average of 5.18 ± 0.10 ($p < 0.05$).

An additional four dogs, subjected to thrombin challenge during RES inhibition but not reported, were unable to withstand the thrombin challenge and died of apparent cardiovascular failure during the thrombin infusion or shortly thereafter. None of the dogs in the thrombin-only, RE blockade, or saline challenged groups died during the four-hour experimental period indicating increased sensitivity to intravascular coagulation in the presence of RES blockade.

Discussion

The participation of the RES in the removal and digestion of circulating abnormal particulates has received much attention.[19–21,23,24] In this regard, the RES has been shown to mediate the vascular clearance of products of the coagulation system such as fibrin,[13] fibrin degradation products,[10] fibrin–fibrinogen complexes and damaged or aggregated platelets.[12] The lung localization of platelets, fibrin and colloidal lipid has been shown to increase following challenge with these substances during reticuloendothelial blockade.[12] This may be due to nonspecific vascular localization or to uptake by specific cells in the lung, but the exact mechanism of entrapment in the lung remains to be determined.

Since the localization of fibrin, fibrin degradation products and platelets in the pulmonary circulation has been related to the development of ventilation perfusion imbalance and pulmonary edema,[16,29] the present study was designed to determine whether inhibition of reticuloendothelial phagocytic clearance could exacerbate the pulmonary insufficiency produced as a result of stimulated intravascular coagulation. The data of this study support the conclusion that RE blockade by itself had minimal effects on pulmonary gas exchange or hemodynamics. Within the time frame of the present protocol, RE blockade had no significant effect on pulmonary venous admixture or on pulmonary blood

TABLE 3. *Pulmonary Gas Exchange in Dogs Subjected to Thrombin Infusion in the Presence of Fibrinolytic Blockade**

Parameters†	Control	1 Hour Post-thrombin	2 Hours Post-thrombin	3 Hours Post-thrombin	4 Hours Post-thrombin
Pa_{O_2}‡	91.1 ± 2.9	76.5 ± 2.5	81.9 ± 2.9	80.3 ± 3.9	75.2 ± 4.0
Pv_{O_2}§	48.9 ± 1.9	41.2 ± 2.5	44.1 ± 2.0	42.1 ± 2.0	39.8 ± 2.5
Pa_{CO_2}‖	37.1 ± 2.1	33.5 ± 2.7	30.4 ± 2.5	29.0 ± 1.1	28.3 ± 2.4
pH¶	7.37 ± 0.02	7.27 ± 0.06	7.31 ± 0.05	7.36 ± 0.04	7.35 ± 0.03
Ca_{O_2}#	19.0 ± 0.3	18.2 ± 0.3	18.4 ± 0.6	18.5 ± 0.5	18.2 ± 0.6
Cv_{O_2}**	14.6 ± 0.6	11.2 ± 1.4	13.1 ± 0.7	12.8 ± 0.8	12.2 ± 1.0
Cc'_{O_2}‡‡	19.6 ± 0.3	19.5 ± 0.3	19.5 ± 0.4	19.7 ± 0.3	19.6 ± 0.3
$\dot{Q}_s/\dot{Q}_t$§§	11.6 ± 1.4	15.2 ± 1.4	16.7 ± 3.1	15.5 ± 3.2	18.6 ± 2.9
$\dot{Q}_t$‖‖	2.5 ± 0.5	2.1 ± 0.6	2.4 ± 0.5	2.2 ± 0.5	2.1 ± 0.5

* Values are expressed as mean ± 1 SEM (n = 4).

† Key to symbols: ‡ Arterial oxygen tension (mmHg). § Mixed venous oxygen tension (mmHg). ‖ Arterial CO_2 tension (mmHg). ¶ Arterial pH. # Arterial oxygen content (volumes per cent). ** Mixed venous oxygen content (volumes per cent). ‡‡ Alveolar end capillary oxygen content (volumes per cent). §§ Pulmonary venous admixture (per cent), ‖‖ Cardiac output (L/min).

TABLE 4. *Pulmonary Gas Exchange in Dogs Subjected to Thrombin Infusion During RES Phagocytic Blockade and with Fibrinolytic Blockade**

Parameters†	Control	1 Hour Post-thrombin & RES Blockade	2 Hours Post-thrombin & RES Blockade	3 Hours Post-thrombin & RES Blockade	4 Hours Post-thrombin & RES Blockade
Pa_{O_2}‡	94.3 ± 5.2	73.9 ± 7.8	64.9 ± 7.0	64.9 ± 6.8	67.9 ± 7.2
Pv_{O_2}§	44.6 ± 1.2	34.1 ± 6.4	38.0 ± 3.5	34.5 ± 1.9	34.1 ± 2.7
Pa_{CO_2}‖	28.0 ± 1.5	28.8 ± 1.0	31.7 ± 4.0	31.6 ± 4.6	29.3 ± 3.8
pH¶	7.38 ± 0.02	7.29 ± 0.01	7.22 ± 0.04	7.21 ± 0.02	7.24 ± 0.01
Ca_{O_2}#	19.8 ± 0.5	17.9 ± 0.9	15.8 ± 1.5	15.9 ± 1.2	16.6 ± 1.9
Cv_{O_2}**	14.7 ± 0.4	9.8 ± 2.7	10.6 ± 1.5	8.8 ± 0.7	8.8 ± 1.6
Cc'_{O_2}‡‡	20.3 ± 0.4	20.2 ± 0.5	19.9 ± 0.4	20.0 ± 0.4	20.1 ± 0.5
$\dot{Q}_s/\dot{Q}_t$§§	9.4 ± 3.0	21.5 ± 5.1	41.5 ± 8.8	36.8 ± 8.4	29.3 ± 10.1
$\dot{Q}_t$‖‖	2.1 ± 0.4	1.8 ± 0.2	1.9 ± 0.2	1.6 ± 0.1	1.5 ± 0.2

* Values are expressed as mean ± 1 SEM (n = 4).

† Key to symbols: ‡ Arterial oxygen tension (mmHg). § Mixed venous oxygen tension (mmHg). ‖ Arterial CO_2 tension (mmHg). ¶ Arterial pH. # Arterial oxygen content (volumes per cent). ** Mixed venous oxygen content (volumes per cent). ‡‡ Alveolar end capillary oxygen content (volumes per cent). §§ Pulmonary venous admixture (per cent). ‖‖ Cardiac output (L/min).

flow. Furthermore, RE blockade alone produced no significant change in physiologic dead space during the study. The absence of any acute rise in pulmonary vascular resistance after lipid administration supports the conclusion that only a relatively small fraction of the lipid was localized within the lung. This is consistent with the observation that less than 1–3% of the injected gelatinized RE test lipid emulsion is localized in the lungs of normal animals.[5,19–22] When compared to the sham infused control group, the low lung wet-to-dry weight ratios in this group suggest that opsonic depletion and RE blockade[2,5,19,20] by itself without an additional stress, *i.e.*, intravascular coagulation, does not produce a significant degree of pulmonary edema.

Those animals subjected to thrombin infusion during fibrinolytic inhibition underwent a rapid and significant rise in pulmonary vascular resistance which was maximal by one hour after infusion. This transient elevation did not coincide with any marked change in either venous admixture or dead space ventilation, suggesting that the dosage of thrombin employed was, in the absence of RE blockade, insufficient to produce a marked decline in gas exchanging efficiency during the study. The elevated lung wet-to-dry weight ratios in this group do suggest the presence of some degree of interstitial pulmonary edema. Increased lung extravascular fluid

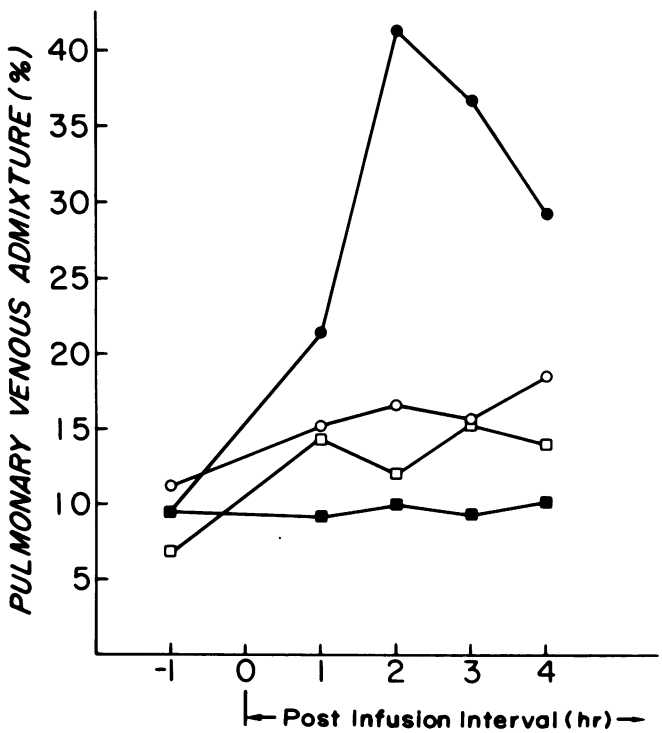

FIG. 5. Pulmonary venous admixture as influenced by thrombin infusion with and without associated RE inhibition. When compared to prechallenge control levels, the greatest increases in shunt were seen in those animals infused with thrombin after the induction of reticuloendothelial blockade. □: Sham infused controls. ■: RE blockade. ○: Thrombin. ●: Thrombin during RE blockade.

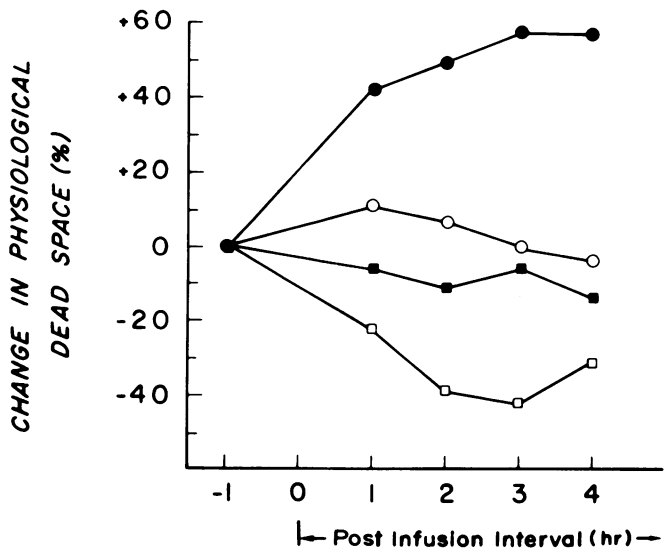

FIG. 6. Changes in physiologic dead space ($\Delta V_D/V_T$) as influenced by thrombin infusion with and without associated RE inhibition, expressed as percent of change. When compared to prechallenge levels, the largest increases in V_D/V_T were seen in the group subjected to thrombin during RE blockade. Neither thrombin alone nor RE blockade alone produced any sustained change in dead space ventilation. □: Sham infused controls. ■: RE blockade. ○: Thrombin. ●: Thrombin during RE blockade.

after thrombin infusion has also been reported by Malik and van der Zee,[17] Lindquist and co-workers.[15]

The experimental group challenged with thrombin in the presence of RE phagocytic blockade underwent the greatest increases in pulmonary vascular resistance after thrombin infusion. Since the cardiac output was not significantly depressed in either of the thrombin challenged groups during the study, it can be concluded that the differences in pulmonary vascular resistances seen between the nonblockaded and RE blockaded thrombin challenged groups was not due solely to differences in perfusion. The sustained increase in PVR at two, three and four hours in the RES blockaded group given thrombin suggests an augmented degree of lung thromboembolization in comparison to the thrombin-only group. An alternative explanation for the marked difference in PVR between the two thrombin challenged groups may relate to the effects of plasma opsonic protein (fibrinonectin) depletion on local intravascular phagocytosis within the pulmonary circulation. Since macrophage phagocytosis is dependent on opsonic glycoprotein coating of particulate material,[20] it is possible that the opsonic depletion induced by the infusion of the gelatin coated particles[2,19,20] inhibited the local macrophage clearance of intravascular debris in the pulmonary microcirculation. Hence, the decline in pulmonary perfusion pressures at two, three and four hours in the thrombin-only group may have been the result of an opsonin-mediated phagocytic clearance of fibrin debris from the pulmonary microcirculation. Differences in intravascular fibrinolysis could not explain these differences, since the fibrinolytic pathway was inhibited with AMCA in both groups.

The hypothesis that RE blockade augmented the lung localization of microaggregates is supported by the marked elevations in physiologic dead space seen in this group, since emboli of sufficient size might be expected to obstruct or abolish perfusion to ventilated lung regions. The elevated venous admixture measurements also tend to support this theory, since ventilation–perfusion imbalance can result from lung embolization, as shown by Dantzker and co-workers.[6] The elevated lung wet-to-dry weight ratios in combination with the elevated dead space measurements and the increased venous admixture in the thrombin-plus-RE blockade group suggest that progressive pulmonary alveolar edema may have been responsible for the impaired gas exchange. With the development of alveolar edema, both an increase in dead space ventilation and an augmentation in pulmonary shunting would be expected. The relative absence of gas exchanging impairment in association with the lower wet-to-dry weight ratios in the thrombin-only animals implies that interstitial but not alveolar edema was present in this group.

Since microembolization of the lung is known to produce bronchoconstriction[29] it is possible that some of

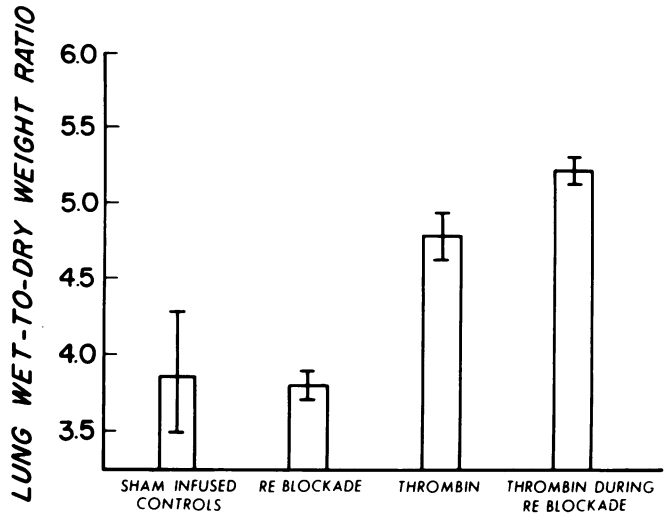

FIG. 7. Lung wet-to-dry weight ratios were measured to provide an index of lung water accumulation. While both groups challenged with thrombin exhibited significantly greater wet-to-dry weight ratios than the saline infused controls, the animals administered thrombin during RES blockade were significantly higher than those given only the thrombin ($p < 0.05$).

the increase in venous admixture may be attributable to the development of low ventilation-perfusion regions secondary to airway restriction. The possible contribution of an alveolar-end capillary diffusion disequilibrium to the hypoxemia cannot be ruled out, since the alveolar oxygen tensions in low ventilation-perfusion regions during room air breathing might be expected to be below 50 mmHg.

In the present study, we cannot distinguish between ventilation to lung regions with attenuated perfusion in relationship to their ventilation (high $\dot{V}_A/\dot{Q}$) and ventilation to nonperfused regions due to the solubility limitations of carbon dioxide. Similarly, during room air breathing the venous admixture measured with oxygen is incapable of resolving areas of low ventilation-perfusion from shunt. Further studies using the inert gas elimination technique of Wagner and West[8] may be necessary to clarify the mechanisms by which thrombin stimulation of intravascular coagulation can disrupt gas exchange in the lung.

Reticuloendothelial phagocytic blockade may augment lung localization of microemboli through two possible mechanisms. Since phagocytosis of circulating aggregates of fibrin, platelets and fibrin degradation products is inhibited during RES dysfunction,[12,13] lung localization may occur as a consequence of the slowed hepatic phagocytosis of such products from the circulation. In addition, since the RE system has been shown to clear activated thrombin from the circulation,[10] reticuloendothelial blockade can increase the half-life of circulating thrombin which could initiate a greater degree of defibrinogenation for a given thrombin dose. Close analysis of the data of Busch and Saldeen[4] sup-

ports this hypothesis, as they found a lower degree of fibrin deposition in extrahepatic tissues after intraportal as compared to intravenous or intra-aortal administration of thrombin. Additionally, our findings of lower fibrinogen levels in animals challenged with thrombin in conjunction with RE blockade as opposed to thrombin alone lend credence to this concept and further emphasizes the role of the RES in homeostatic control of hemostasis.

The role of opsonic glycoprotein (plasma fibronectin) depletion in colloid induced RE blockade has been shown.[3,19,20] Although serum opsonin has been shown to decrease significantly during colloidal lipid induced blockade,[2] the role of opsonin in the clearance of thrombin and fibrin needs further investigation. Opsonic protein, which is identical to plasma fibronectin or cold-insoluble globulin (CIg)[23,24] is depleted during intravascular coagulation in humans,[18] and its level appears to correlate with organ failure after injury or with sepsis.[24,26] Indeed, the conclusions of the present study are supported by recent studies of opsonic glycoprotein replacement therapy in septic trauma and surgical patients.[24,26] In these studies, a deficiency of bioassayable and immunoreactive opsonic α_2SB glycoprotein was shown to exist, especially during sepsis coexisting with multiple organ failure.[24,26] Opsonic α_2SB glycoprotein is identical to cold-insoluble globulin or plasma fibronectin[23] and thus concentrated in plasma cryoprecipitate.[24,26] Infusion of cryoprecipitate will reverse the opsonic deficiency, augment reticuloendothelial host defense, and decrease in both intrapulmonary shunt and dead space ventilation.[24,26]

Thus, in conclusion, RES depression results in a potentiation of the pulmonary gas exchange and hemodynamic abnormalities after thrombin infusion. This may be due to its failure to clear particulate matter as well as circulating activated thrombin. This may be of significance in the etiology of pulmonary insufficiency following trauma and burn, especially during sepsis, which has been documented to result in reticuloendothelial depression.[24–26] The recent clinical studies by Mosher and Williams[18] on the presence of plasma fibronectin deficiency in association with organ failure during disseminated intravascular coagulation further emphasizes the clinical importance of the reticuloendothelial system with respect to cardiopulmonary function.[20,22,24] It is suggested that the relationship between RES failure and pulmonary injury warrants investigation from the standpoint of its clinical importance as well as its physiological implications.

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