Effect of furosemide in canine low-pressure pulmonary edema.

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Research Article

We studied the effect of furosemide on pulmonary oxygen exchange, lung liquid, and central hemodynamics in dogs with pulmonary capillary leak induced by intravenous oleic acid (OA). 2 h after OA, triple indicator-dilution lung liquid volume and pulmonary shunt (Qs/Qt) doubled despite normal pulmonary capillary wedge pressure in 16 dogs compared with dogs not given OA in which no variable change during the same time. Six edematous dogs were then treated with furosemide (1 mg/kg), and 2 h later they showed significant reductions in Qs/Qt and lung liquid. In contrast, six other edematous dogs not given furosemide increased Qs/Qt and lung liquid during the same time. The changes in edema after furosemide could not be attributed to altered wedge or colloid osmotic pressures, and similar changes in Qs/Qt and lung liquid with furosemide were observed in four nephrectomized dogs. We conclude that pulmonary vasoactive effects of furosemide account for reduced shunt and edema in canine pulmonary capillary leak. These effects of furosemide differ from those in cardiogenic pulmonary edema, and suggest a different rationale for diuretic therapy in low-pressure pulmonary edema. Analysis of count rates from 51Cr-labeled erythrocytes and 125I-labeled albumin in lungs excised from 12 dogs indicated that the composition of excess lung liquid did not change with furosemide, and was 50% plasma, 25% blood, and 25% crystalloid.

Effect of Furosemide in Canine Low-Pressure Pulmonary Edema

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ABSTRACT We studied the effect of furosemide on pulmonary oxygen exchange, lung liquid, and central hemodynamics in dogs with pulmonary capillary leak induced by intravenous oleic acid (OA). 2 h after OA, triple indicator-dilution lung liquid volume and pulmonary shunt (Qs/Qt) doubled despite normal pulmonary capillary wedge pressure in 16 dogs compared with dogs not given OA in which no variable change during the same time. Six edematous dogs were then treated with furosemide (1 mg/kg), and 2 h later they showed significant reductions in Qs/Qt and lung liquid. In contrast, six other edematous dogs not given furosemide increased Qs/Qt and lung liquid during the same time. The changes in edema after furosemide could not be attributed to altered wedge or colloid osmotic pressures, and similar changes in Qs/Qt and lung liquid with furosemide were observed in four nephrectomized dogs. We conclude that pulmonary vasoactive effects of furosemide account for reduced shunt and edema in canine pulmonary capillary leak. These effects of furosemide differ from those in cardiogenic pulmonary edema, and suggest a different rationale for diuretic therapy in low-pressure pulmonary edema. Analysis of count rates from ^{51}Cr-labeled erythrocytes and ^{125}I-labeled albumin in lungs excised from 12 dogs indicated that the composition of excess lung liquid did not change with furosemide, and was 50% plasma, 25% blood, and 25% crystalloid.

INTRODUCTION

Diuretics have long been used to treat pulmonary edema secondary to left heart failure. Their effectiveness is attributable to the reduced filling pressure of the left heart and pulmonary capillaries, which results when central blood volume is reduced by diuresis and by the diuretic enhanced capacitance of the systemic venous bed (1–6). Conceivably, such other mechanisms as increased plasma oncotic pressure or increased pulmonary lymph flow also reduce the pulmonary edema. Another form of pulmonary edema in which there is no evidence of left heart failure and the pulmonary capillary pressure is normal or low is now frequently recognized (7, 8). Increased permeability of the pulmonary capillary to plasma constituents has been proposed to explain this disorder, and several animal models have been developed which simulate aspects of it. After the intravenous injection of oleic acid in dogs, hemorrhagic pulmonary edema and severe hypoxemia secondary to true intrapulmonary shunt develop in the absence of elevated pulmonary artery wedge pressure (9). The histopathologic changes and the hypoxemia seen in this model closely resemble the findings in human subjects dying from posttraumatic pulmonary insufficiency (9). This study was designed to determine whether furosemide alters the course of low-pressure pulmonary edema by studying the canine oleic acid model, and to determine if this alteration is related to diuresis.

GLOSSARY OF SYMBOLS

Groups of dogs	
OA	Oleic acid only
OA + NE + F	Oleic acid, nephrectomy, and furosemide
OA + F	Oleic acid, furosemide, intact kidneys
F	Furosemide only
Pulmonary gas exchange	
P_EO_2	Partial pressure of oxygen in mixed expired gas
P_ECO_2	Partial pressure of carbon dioxide in mixed expired gas
P_AO_2	Alveolar partial pressure of oxygen
PaO_2	Arterial partial pressure of oxygen
$PaCO_2$	Arterial partial pressure of carbon dioxide
CaO_2	Oxygen content in arterial blood
CvO_2	Oxygen content in mixed venous blood
$Cc'O_2$	Oxygen content of pulmonary capillary blood
Indicator dilution techniques	
Qs/Qt	Pulmonary shunt fraction
CBV	Central blood volume(s)
Vw	Pulmonary extravascular lung water
HTO	Tritiated water
$\bar{t}$	Mean transit time

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Q	Blood flow
fB	Water content of blood at central hematocrit
Assessment of lung liquid composition	
WW	Wet weight of lung
V_H	Homogenate volume
C_B	Counts per minute per milliliter in a 0.5-ml aliquot of blood
C_H	Counts per minute per milliliter in a 2-ml aliquot of lung homogenate
V_B	Volume of blood in the excised lung
V_P	Difference in V_B between ^{51}Cr and ^{125}I representing lung plasma in excess of lung blood
DW	Dry weight of lung
Vwa	Actual extravascular water content
W/D	Wet:dry weight ratio(s)
Hemodynamics and lung liquid flux	
Q_E	Net flow of lung liquid
Q lymph	Pulmonary lymphatic flow
Kf	Pulmonary microvascular permeability coefficient
σ	Reflection coefficient of the capillary membrane
Pmv	Pulmonary microvascular hydrostatic pressure
Pis	Pulmonary interstitial hydrostatic pressure(s)
πmv	Pulmonary microvascular colloid osmotic pressure
$\pi$is	Pulmonary interstitial colloid osmotic pressure
P_{La}	Left atrial pressure(s)
Ppa	Mean pulmonary artery pressure
Ppw	Pulmonary artery wedge pressure
Qt	Cardiac output
PVR	Pulmonary vascular resistance
Palv	Alveolar pressure

METHODS

20 healthy mongrel dogs weighing between 14 and 29 kg were studied. Each was anesthetized with pentobarbital (29 mg/kg), and ventilated with oxygen and halothane (0.5%) with a tidal volume of 20 cm^3/kg and a respiratory rate of 15/min. Each animal was heparinized with 200 IU of sodium heparin/kg body wt. Polyethylene catheters were placed in the femoral artery and vein, and a thermal dilution Swan-Ganz catheter (Edwards Laboratories, Inc., Santa Ana, Calif.) was positioned in the pulmonary artery. A French Foley catheter (No. 14, Edwards Laboratories, Inc.) was inserted in the bladder by cystostomy. All animals had a midline abdominal incision through which both kidneys were mobilized. In a group of four dogs (group OA + NE + F), the renal pedicles were completely ligated causing effective nephrectomy whereas in the others the kidneys were not altered other than the mobilization procedure.

After control measurements, OA (0.06 ml/kg) was injected intravenously in three groups of dogs (group OA, group OA + NE + F, and group OA + F). Measurements were made after 2 h, and then furosemide (1 mg/kg) was injected intravenously in group OA + NE + F, group OA + F and group F. Group OA animals received no furosemide. Group OA and group OA + F consisted of six animals each, and the fourth group (group F), which consisted of four animals, received furosemide only. The measurements were repeated at 4 h (i.e., 2 h postfurosemide). This design allowed assessment of the effect of furosemide on OA pulmonary edema by comparing 2- and 4-h measurements in intact dogs (group OA vs. group OA + F) and nephrectomized dogs (group OA vs. group OA + NE + F).

Pulmonary artery (Ppa), pulmonary wedge (Ppw), and systemic blood pressure were measured with Statham vascular pressure transducers (P23 DB and BB, Statham Instruments, Inc., Oxnard, Calif.) coupled to a multichannel Beckman Oscillographic recorder (Beckman Instruments, Inc., Fullerton, Calif.). Cardiac output (Qt) was measured by thermodilution (Columbus Instruments, Columbus, Ohio), and pulmonary vascular resistance (PVR) was calculated: PVR = (Ppa − Ppw)/Qt. Arterial and mixed venous blood samples were collected in heparinized syringes and analyzed immediately for pH, P_{CO_2}, and P_{O_2} on a Corning 165-2 blood gas analyzer (Corning Glass Works, Corning, N. Y.), and for hemoglobin concentration (Hb, grams per 100 milliliters). Mixed expired gases were collected and analyzed for P_EO_2 and P_ECO_2 using the same electrodes, and these values were used to estimate pulmonary capillary and alveolar O_2 tension ($P_AO_2 = P_EO_2 + P_ECO_2 - PaCO_2$). Blood gas tensions were corrected to blood temperature, and oxygen saturations were calculated using the nomogram of Rossing and Cain (10). Oxygen contents in arterial (CaO_2), mixed venous (CvO_2), and pulmonary capillary ($Cc'O_2$) blood were calculated as: percent saturation × (Hb, g/100 ml × 1.34) + P_{O_2} × 0.003. These were used to estimate shunt (Qs/Qt). $Qs/Qt = (Cc'O_2 - CaO_2)/(Cc'O_2 - CvO_2)$. Serum albumin, globulin, and total proteins were also measured in arterial blood by the Biuret and bromo-cresol green techniques.

Estimates of central blood volume (CBV) and pulmonary extravascular lung water (Vw) were made at control, 2, and 4 h in four animals from each group according to indicator-dilution techniques described in detail by Kirk (11). Briefly, a solution of ^{51}Cr-labeled erythrocytes (30 mCi), ^{125}I-labeled human serum albumin (8 mCi), and tritiated water (HTO) (25 mCi) was injected into the right ventricle and sampled at 1-s intervals from the root of the aorta. ^{51}Cr- and ^{125}I-gamma activities of an ethanol precipitate were determined in a 400-channel analyzer with corrections for background and spillover, and HTO activity was determined in an ethanol extract by a Nuclear-Chicago MKl liquid scintillation counter (Nuclear-Chicago Corp., Des Plaines, Ill). Assuming that erythrocytes do not leave the circulation in a single pass, we calculated blood flow (Q) from the dilution curves for ^{51}Cr. CBV was calculated by the product of Q and the mean transit time ($\bar{t}$) of cells, and represents the volume of blood from the right ventricle to the root of the aorta. Vw was calculated as suggested by Chinard et al. (12) where $Vw = (Q \cdot \bar{t}\ HTO) - CBV$ fB, and fB is the water content of blood at the central hematocrit.

The liquid composition of excised lungs was determined (11). 20 min after the final dilution curve in each animal, blood samples were drawn for final blood activity of ^{51}Cr and ^{125}I. The thorax was opened rapidly through a median sternotomy. Clamps were placed on the lung hilae, and the lungs that contained blood were excised and weighed wet (WW). They were then homogenized in a Waring blender (Waring Products Div., New Hartford, Conn.) with 20 ml of distilled water. The homogenate volume (V_H) was measured after overnight settling. Duplicate 2-ml aliquots of lung homogenate and 0.5-ml aliquots of blood were counted for ^{51}Cr and ^{125}I, expressed as counts per minute per milliliter of each (C_B, C_H). The volume of blood (V_B) in the excised lungs was then calculated for each isotope. $V_B = (C_H \cdot V_H)/C_B$. We assumed that differences in V_B between ^{51}Cr and ^{125}I represent a different volume of distribution of cells and plasma within the lung, and expressed this difference as lung plasma in excess of lung blood (V_P).

The remaining homogenate was dried to a constant weight in a vacuum oven at 60°C and 400 torr of absolute pressure to obtain dry weight (DW). To normalize for variations in lung size, all estimates of lung liquid components in grams or milliliters (WW, DW, V_B, Vwa, CBV, and Vw) were expressed as a ratio of body weight in kilograms.

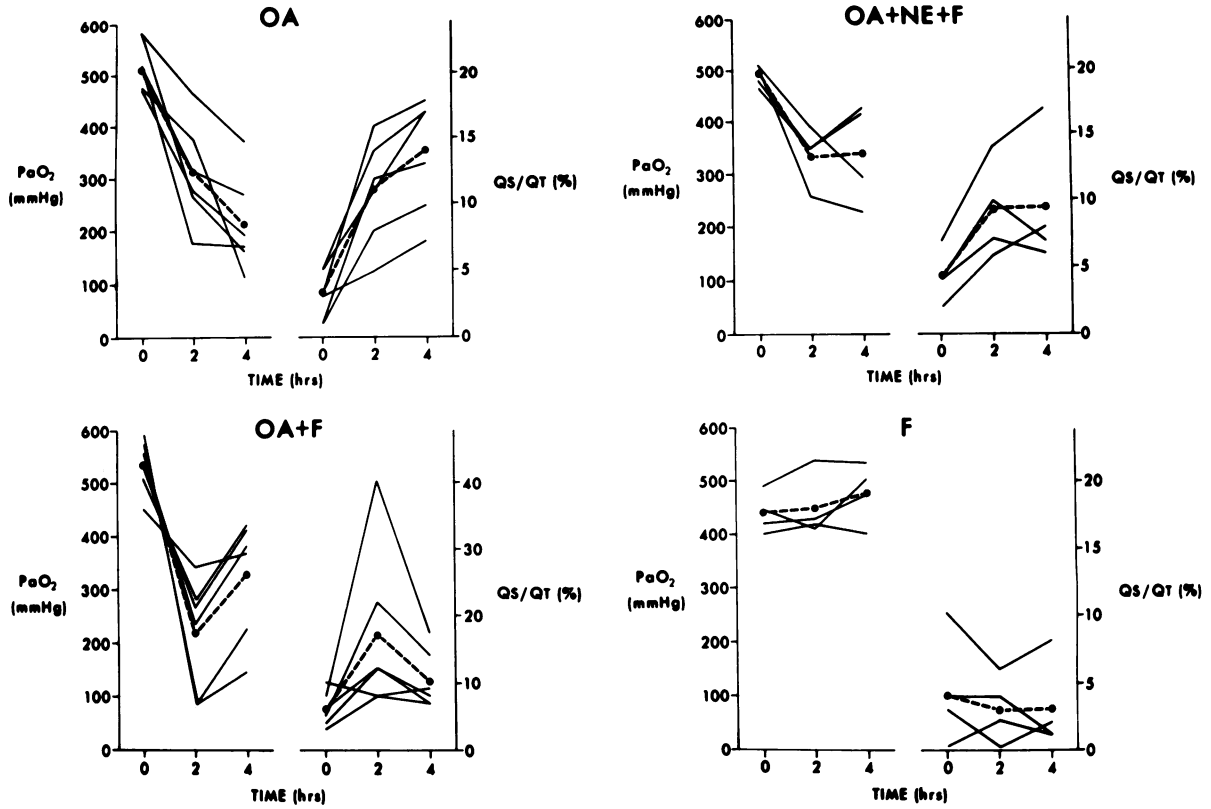

FIGURE 1 Effects of OA and furosemide on PaO_2 (left ordinate) and Qs/Qt (right ordinate) in four experimental groups. Solid lines (individual values) and interrupted lines (group mean values) connect base-line measurements (0 h) and measurements repeated at 2 and 4 h. Group OA received OA only. Group OA + NE + F was nephrectomized and received OA and furosemide 2 h after OA. Group OA + F with intact kidneys received furosemide 2 h after OA. Group F had furosemide and no OA. For discussion, see text.

RESULTS

Fig. 1 shows the effect of OA and furosemide in PaO_2. The mean values of PaO_2 (mmHg) at the start of the study (time 0) were 524±19 (group OA), 494±20 (group OA + NE + F), 533±51 (group OA + F), and 439±37 (group F). These values were not significantly different among groups by analysis of variance. In all groups receiving OA, PaO_2 decreased significantly by 2 h ($P < 0.01$), but it did not change in group F (no OA) (Fig. 1). 2 h after furosemide, all group OA + F animals showed an increase in PaO_2, and the mean values increased from 215±45 to 327±47 ($P < 0.01$). In contrast, all animals in group OA (no furosemide) had decreased PaO_2 during the same period, and the mean PaO_2 decreased from 308±41 to 211±39 ($P < 0.05$). In group OA + NE + F (nephrectomy), PaO_2 did not change after furosemide (339±97) from the value 2 h after OA (335±48). There were no obvious trends in PaO_2 in group F between time 0 and 2 h, and furosemide caused no change in PaO_2. No significant changes in $PaCO_2$ or pH were observed in any group throughout the study, and these averaged 35±3 and 7.34±0.04, respectively.

These changes in PaO_2 were associated with changes in Qs/Qt (Fig. 1), which increased in all animals receiving OA. After furosemide, five of six dogs in group OA + F had reduced Qs/Qt, and the mean value decreased from 0.17±0.12 to 0.10±0.04 ($0.05 < P < 0.1$). All dogs in group OA increased their shunt during the same time, and mean Qs/Qt increased from 0.11±0.04 to 0.14±0.04 ($P < 0.05$).

Table I summarizes the effects of OA and furosemide on the central hemodynamics. During the 2 h after OA injection, Qt and Ppw tended to decrease in all groups including the control group (F), and PVR tended to increase. A continuation of these trends was observed in all groups after furosemide.[1] Note the statistically

[1] The spontaneous changes in Qt at 4 h and Ppw at 2 h in group F were not associated with alteration in gas exchange. In group OA, deterioration in gas exchange at 2 h was not associated with a significant fall in Qt, whereas in group

TABLE I
*Effect of OA and Furosemide on Central Hemodynamics**

Group	Qt			Ppw			PVR		
	Control	2 h	4 h	Control	2 h	4 h	Control	2 h	4 h
	liters/min			*mm Hg*			*mm Hg/liter/min*		
OA	2.14±0.82	2.05±1.45	1.66±0.94	7.3±2.0	6.0±2.1	4.5‡±1.4	3.2±1.3	5.0±3.0	6.1±2.6
OA + NE + F	1.26±0.19	0.89‡±0.02	0.76±0.12	8.3±1.3	6.8‡±1.5	6.5±1.3	4.3±1.1	7.3‡±1.2	11.0‡±0.9
OA + F	3.16±1.30	1.87‡±0.73	1.59‡±0.63	9.3±3.1	8.2±2.9	7.5±3.6	2.6±1.2	4.6±2.6	7.4‡±6.4
F	1.71±0.27	1.30±0.18	1.04‡±0.17	8.5±1.0	6.0‡±0.8	5.5±1.0	3.2±0.52	4.6±1.04	6.2‡±1.0

* Mean±SD.
‡ Denotes significance ($P < 0.05$) from the preceding measurement.

significant reduction in Ppw between 2 and 4 h in group OA (no furosemide) compared with a smaller and insignificant fall in group OA + F. Both groups showed similar mean reduction in Qt, although this trend in group OA was not statistically significant ($0.05 < P < 0.1$). PVR increased in all groups receiving furosemide, but the mean increase in group OA (no furosemide) was smaller and not statistically significant.

Urine output was similar in all nonnephrectomized groups before and after OA, and increased considerably after furosemide (Table II). Compared with group OA, there was a 300-ml greater urine output in group OA + F during the 2 h after furosemide. This was associated with reduced mean Qs/Qt and increased mean PaO_2 without lowering mean Ppw as much as in group OA. Furthermore, even with no urine output after furosemide, the nephrectomized dogs (group OA + NE + F) did not increase their shunt or decrease their PaO_2 as did the dogs in group OA.

Table III summarizes the results of serum albumin and globulin measurements and analysis. There were no differences among groups at time 0 (control), and both proteins tended to decrease slightly by 2 and 4 h. These trends were not significant in any group, and there were no differences among groups after OA or after furosemide.

WW and DW from the four dogs not given OA (group F) did not vary much (Table IV). All of these values are within the normal range, and the mean wet:dry weight ratio (W/D) was 3.85. As calculated from the ^{51}Cr-labeled erythrocyte activity in the excised lung homogenate, about one-third (3.2 ml/kg) of the WW (9.4 g/kg) was blood (V_B). The lung blood was also calculated from ^{125}I-labeled albumin in the lung homogenate. These values are expressed in Table IV (V_P, ml/kg) as the lung blood calculated from ^{125}I less the $[^{51}Cr]V_B$. The small difference between these two estimates of lung blood volume in each normal dog averaged zero, which indicates that lung blood and plasma were in the same proportion as in the vascular space. Blood-free extravascular lung water averaged 6.2 ml/kg body wt (Table IV, H_2O ml/kg). In these four dogs the hematocrit at the end of the experiment ranged from 46 to 60%, and gave blood W/D values from 3.9 to 2.9, and the blood-free lung W/D values ranged from 3.5 to 4.5 (mean 4.07).

The excised lungs of 12 dogs given OA had doubled WW and a small increase in DW (Table IV) compared with group F. The W/D were larger in all dogs receiving furosemide after OA (group OA + F) than in all dogs receiving only OA. In the nine OA treated dogs in which estimates of lung blood were obtained with both ^{51}Cr-labeled erythrocytes and ^{125}I-labeled albumin, the mean WW was 20.9±2.7 (Table IV). The difference

OA + NE + F and group OA + F, there was significant depression of Qt in association with the deteriorating Qs/Qt at 2 h. A fall in Qs/Qt in OA pulmonary edema is known to accompany a decrease in Qt (13), and, because there was no such decrease in shunt with the decreased Qt in these groups, there must be other factors responsible for the change in shunt. The further fall in Qt at 4 h in group OA + F is, therefore, not entirely responsible for the decreased shunt. Overall examination of the hemodynamic data shows that the trends were the same in all the measured parameters for all groups, yet the changes in shunt did not follow this pattern. It would appear, therefore, that these hemodynamic changes, though important, are not crucial to the understanding of the action of furosemide in this study of low-pressure pulmonary edema.

TABLE II
Urine Output

Group	1 h*	2 h	3 h	4 h
		ml		
OA	43±13‡	38±10	37±12	34±18
OA + NE + F	0	0	0	0
OA + F	29±10	33±15	177±68	201±48
F	29±10	43±21	128±62	155±21

* Hourly collections at times after OA injection.
‡ Mean±SD.

TABLE III
*Serum Protein Concentrations in All Four Groups of Animals**

Groups	Control		2 h		4 h	
	Albumin	Globulin	Albumin	Globulin	Albumin	Globulin
			gm/dl			
OA	2.1±0.1	3.5±0.6	1.9±0.2	3.5±0.1	1.7±0.2	3.4±0.4
OA + NE + F	2.0±0.2	3.4±0.4	1.7±0.3	3.1±0.4	1.7±0.3	3.0±0.3
OA + F	2.2±0.2	3.4±0.3	2.0±0.2	3.4±0.3	1.9±0.2	3.3±0.1
F	1.8±0.2	3.8±0.4	1.7±0.1	3.6±0.3	1.6±0.2	3.7±0.3

* Mean±SD.

between this mean and the corresponding mean WW in group F indicates that OA caused ≅11.5 ml/kg of excess lung liquid. Blood accounted for 6.2±2.4 ml/kg of the WW in those nine OA-treated dogs, which indicates an average increase in lung blood after OA of 3.0 ml/kg compared with group F. This blood may be interstitial or intravascular and accounted for about one-quarter of the excess of lung liquid. There was no obvious difference in the amount of excess blood among OA, OA + NE + F, and OA + F.

In each of these dogs, the lung blood calculated from ^{125}I exceeded that calculated from ^{51}Cr (Table IV). We assumed that this indicated greater plasma than blood leak, and we tabulated the difference between these values as the plasma leak in excess of blood leak (V_P). This averaged 5.3 ml/kg after OA and 0 ml/kg in group F, which indicates that OA caused a leak of cell-free plasma accounting for about one-half of the excess lung liquid. Again, there was no obvious difference in plasma leak among the other groups. The remaining 28% of the

TABLE IV
Weights and Composition of Excised Lungs

	Lung weights			Lung composition		
	W/D	DW	WW	Blood	V_P	H_2O
		ml/kg body wt		*ml/kg body wt*		*ml/kg body wt*
Group F	4.15	2.0	8.3	2.4	−0.1	6.0
	3.91	2.2	8.6	2.9	0.2	5.5
	3.65	2.6	9.5	3.3	0.1	6.1
	3.67	3.0	11.0	4.0	−0.3	7.3
Mean (±SD)	3.85±0.24	2.4±0.4	9.4±1.2	3.2±0.7	0±0.22	6.2±0.8
OA groups						
Group OA	5.29	4.8	25.4	6.6	5.6	13.4
	5.24	3.8	20.1	6.1	6.0	8.0
	5.58	3.3	18.4	6.6	—	—
	5.69	4.3	24.6	6.4	6.4	11.8
Group	4.58	3.1	14.2	—	—	—
OA + NE + F	5.22	3.6	18.8	3.7	5.3	9.9
	8.44	2.5	21.1	8.5	2.4	10.3
	5.32	3.7	19.7	7.9	2.7	9.1
Group OA + F	6.32	3.1	19.6	—	—	—
	6.35	2.6	16.5	1.9	8.7	5.9
	7.67	2.7	20.7	5.2	7.0	8.5
	7.57	2.8	21.2	9.9	4.0	7.4
Mean (±SD)	6.31	3.5	20.9	6.2	5.3	9.4
(n = 9)*	(1.26)	(0.8)	(2.7)	(2.4)	(2.0)	(2.3)

* Mean and SD of the nine experiments in the OA group in which all variables in this table were measured.

weight gain after OA was attributed to blood-free, plasma-free lung water excess. Lung water averaged 9.4±2.3 ml/kg in the nine OA-treated dogs in which it could be calculated, and this value exceeds corresponding means in group F by 3.2 ml/kg.

In summary, the excess lung liquid in OA pulmonary edema was composed of about one-quarter whole blood, one-half cell-free plasma, and about one-quarter blood- and plasma-free crystalloid. With the mean W/D values measured for blood (4.0) and plasma (16.0) in these nine dogs, we calculated the DW of the excess liquid to be 1.1 g/kg. This value closely approximated the difference in DW between OA and group F dogs, and gives a W/D of the excess lung liquid of 10.5. These data indicate that OA caused a similar amount and composition of excess lung liquid in all three groups, with the possible exception that W/D of furosemide-treated group OA + F dogs tended to exceed W/D of group OA dogs (no furosemide).

The results of the indicator-dilution studies are illustrated in Fig. 2. CBV (upper panels, milliliters per kilogram) was similar in control conditions for all groups and averaged 15.1±2.2 ml/kg. It decreased progressively with time to 12.1±2.0 at 2 h and to 10.2 ±1.8 at 4 h. The reduction in CBV between 0 and 2 h was quite similar in the group not receiving OA as in the other three groups.[2] Between 2 and 4 h, there were no obvious differences in CBV between group F and the groups given OA. Furthermore, the upper panels of Fig. 2 indicate that groups OA + NE + F and OA + F had a similar reduction in CBV during the 2 h after furosemide, as did group OA (no furosemide). Note that the CBV were quite similar in groups OA and OA + F just before the lungs were excised at the end of the experiment.

Values of Vw (lower panels, milliliters per kilogram) were quite similar in all groups in control conditions,

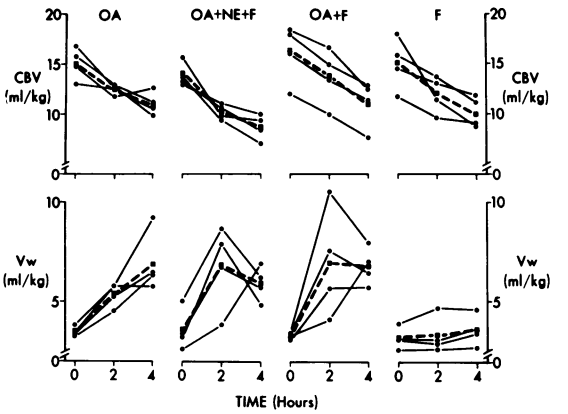

FIGURE 2 Effects of OA and furosemide on CBV (upper ordinate) and indicator-dilution lung liquid (Vw, lower ordinate) in the same four experimental groups. Solid lines (individual values) and interrupted lines (group mean values) connect base-line measurements (0 h) and measurements repeated at 2 and 4 h. Note the similar reduction in CBV with time in all groups, and the increase in Vw in groups given OA (groups OA, OA + NE + F, and OA + F). Vw tends to decrease in the 2 h after furosemide in groups OA + NE + F and OA + F, but tends to increase during the same time in group OA (no furosemide). For discussion, see text.

and averaged 3.37±0.56. There was no obvious change in Vw in group F during the next 4 h (lower right). In contrast, each of the 12 dogs studied 2 h after OA increased Vw, and the mean (±SD) value approximately doubled to 5.35±2.0 ($P < 0.01$). The mean value of Vw was less in group OA (5.36) than in group OA + NE + F (6.79) or group OA + F (6.94). During the next 2 h, three of four group OA dogs increased Vw further (Fig. 2, left lower) and mean Vw in group OA increased to 6.94. During that same time, five of the eight animals in group OA + NE + F and group OA + F decreased Vw after furosemide, and the mean values of these eight experiments tended to decrease from 6.86±2.29 at 2 h to 6.32±0.97 at 4 h. Consequently, values of Vw were quite similar in groups OA and OA + F just before the lungs were excised at 4 h.

To assess the accuracy of in vivo estimates of extravascular lung water by indicator dilution in this study, we plotted Vw against actual extravascular water content (Vwa) of the excised lungs (Fig. 3). Vwa was calculated by subtracting the blood volume of lung from the W/D difference. This underestimates Vwa by the water content of extravascular lung blood. Group F values cluster about the identity line, and the average Vw/Vwa value was 0.95. In contrast, Vwa was underestimated by indicator dilution in all dogs treated with OA. There was no obvious difference in the amount of underestimation in the dogs given furosemide after OA (mean±SD, Vw/Vwa = 0.59±0.08, $n = 6$) from the group OA dogs (mean±SD, Vw/Vwa = 0.61±0.14, $n = 4$). We conclude that our indicator-dilution tech-

[2] CBV changes in the individual groups were compared by analysis of variance. At 0, 2, and 4 h, respectively, the mean and SD for the CBV in the four groups were: 15.2±1.6, 12.4±0.3, and 11.0±1.3 for group OA; 13.8±1.3, 10.1±0.7, and 8.7±1.3 for group OA + NE + F (nephrectomy); 16.3±3.0, 13.7±2.8, and 11.1±2.3 for group OA + F; and 14.9±2.7, 12.1±1.5, and 10.1±1.5 for group F. The F (statistical) value for 0-, 2-, and 4-h comparisons were, respectively: 0.797, 3.24, and 1.77, all of which were not significant. Analysis of variance for the difference between 0 and 2 h and 2–4 h was conducted with the following results: the mean±SD of the difference from 0 to 2 h was 2.9±1.5 for group OA, 3.7±1.8 for group OA + NE + F, 2.6±0.8 for group OA +F, and 2.8±2.6 for group F. The F value was 0.300, which was not significant. The mean ±SD of the differences from 2 to 4 h was 1.4±1.6 for group OA, 1.4±0.9 for group OA + NE + F, 2.6±0.9 for group OA + F, and 2.2±0.5 for group F. The F value was 1.298, which was again not statistically significant. These statistical comparisons of the individual groups, therefore, show that they all behaved in a similar manner as far as CBV changes were concerned.

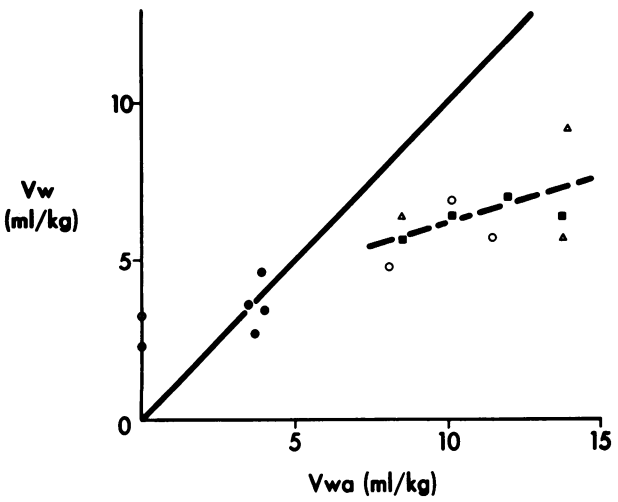

FIGURE 3 Relationship between actual lung liquid (Vwa, abscissa) and indicator-dilution lung liquid at 4 h (Vw, ordinate). Solid circles from group F (no OA) cluster about the continuous line of identity, but Vw values from each of the edematous groups (OA, ■; OA + NE + F, ○; OA + F, △) are ≅0.6 Vwa. The interrupted regression line for these edemtous values is shown (r = 0.63, n = 10). For discussion, see text.

niques underestimated OA pulmonary edema by ≅40%, and this error was not influenced in a major way by furosemide. This underestimate of in vivo lung water may be a reflection of known limitations of indicator-dilution methodology. Because the indicators are all administered intravenously, only perfused areas would be assessed. Edema itself may, however, decrease perfusion by extravascular mechanical compression. Furthermore, with increased capillary permeability in OA hemorrhagic pulmonary edema there is no guarantee that so-called intravascular markers would remain intravascular.

DISCUSSION

Furosemide unequivocally reduced intrapulmonary shunt in dogs with OA pulmonary edema. Even in nephrectomized animals, it prevented the increase in Qs/Qt between 2 and 4 h after OA observed in group OA dogs not given furosemide. By definition, the reduced shunt observed 2 h after furosemide in group OA + F indicates that a smaller fraction of the pulmonary blood flow perfused nonventilated regions. In our model, the most likely cause of nonventilated air space after OA is alveolar flooding with excess lung liquid as demonstrated by the lung liquid in Table IV and Fig. 2. One surprising finding in this study was that the improvement in gas exchange was not obviously associated with reduced pulmonary edema. In fact, the W/D of the excised lungs suggest that edema may be worse in the furosemide-treated group OA + F than in group OA. However, confident assessment of the relative amount of excess lung liquid from our data was more difficult than we anticipated. In the following discussion, we consider several interpretations of the results of excess lung liquid and its composition derived from our in vivo indicator-dilution techniques and our excised lung measurements. We also attempt to relate these considerations to our measurements of factors governing lung liquid in OA pulmonary edema. Finally, we attempt to use the possible conclusions concerning lung liquid balance and central hemodynamic effects of furosemide to explain how furosemide decreased pulmonary shunt.

Amount and composition of excess lung liquid. Of several methods to determine the amount of extravascular lung water, the most direct is to subtract DW and lung blood volume (V_B) from the WW of excised lungs (14). This approach was partially confounded in our study because about one-fourth of the excess lung liquid was blood, which could be intravascular or extravascular. Based on the gross appearance of the excised lung, on the reported histology of canine OA pulmonary edema demonstrating interstitial and alveolar erythrocytes (9), and on the similarity of our CBV estimates in all groups in this study, we think that most of the excess blood is extravascular. Nevertheless, the amount of lung liquid was not obviously different among groups OA + NE + F and OA + F (furosemide) and group OA (no furosemide) when it was estimated (Table IV) as either WW–DW (viz., no intravascular blood) or WW–DW–V_B (viz., all the blood is intravascular). All three OA groups had more than twice the lung liquid content of group F. Accordingly, OA caused hemorrhagic pulmonary edema, and it seems unlikely that there was less lung liquid in excised lungs of the furosemide-treated groups.

An alternative index quantitating pulmonary edema is the W/D. W/D has the potential advantage of normalizing lung liquid volume to an index of lung mass (DW). This was also partially confounded in our study because the total excess extravascular lung liquid contained substantial nonevaporable substance in the form of 25% blood (mean W/D ≅3.5) and a further 50% excess plasma (mean W/D ≅16.0). In the nine OA-treated excised lungs in which blood and plasma content were determined, there were no obvious differences in amount of excess blood or plasma between furosemide-treated groups and group OA (Table IV). Furthermore, furosemide did not influence CBV estimates (Fig. 2). These arguments suggest that the strong trend toward higher W/D in group OA + F than in group OA is not a result of artifacts introduced by variable W/D of edema liquid between the groups, but, rather, indicates that the furosemide groups had more pulmonary edema.

Regardless of whether group OA + F dogs had similar or greater edema than group OA, the in vivo indicator

estimates of Vw suggest that furosemide reduced edema accumulation after OA. Our values of Vw were not accurate in OA edema because the 4-h measurements averaged ≅60% of the actual water content of excised lungs (Fig. 3). Assuming the same relationship (Vw/Vwa × 0.6) at 2 h, mean Vwa would be less in group OA (9.0 ml/kg) than group OA + F (11.5 ml/kg) or group OA + NE + F (11.3 ml/kg). Although the scatter is wide among these 12 dogs, these data suggest the possibility that group OA + F animals received, by chance, a larger OA lesion and developed greater pulmonary edema by 2 h than did group OA animals. Furthermore, during the next 2 h, three of four group OA animals increased Vwa, and the mean value increased to 11.5 ml/kg. In contrast, furosemide treatment was associated with reduced Vwa between 2 and 4 h in five of eight animals in groups OA + NE + F and OA + F, and mean Vwa at 4 h tended to decrease after furosemide. We wondered whether these results might be a result of greater underestimation of Vwa by indicator dilution after furosemide, but the results in Fig. 3 do not support an obviously different Vw/Vwa among the OA groups. Accordingly, our data do not exclude the possibility that furosemide treatment decreased lung water even though the actual water content and W/D of excised lungs was as large or larger in group OA + F than in group OA.

We conclude that our indicator-dilution and excised-lung studies did not clearly demonstrate an effect of furosemide on canine OA pulmonary edema. This shortfall was in part because of the complex composition of OA pulmonary edema, which this study quantitated for the first time. The excess lung liquid measured 4 h after 0.06 ml/kg OA was administered intravenously consisted of ≅50% cell-free plasma, ≅25% whole blood, and ≅25% crystalloid. These findings are consistent with the notion that intravenous OA causes a range of lesions increasing pulmonary vascular permeability to water, plasma proteins, and erythrocytes. One consequence of the observed vascular permeability to plasma proteins is a marked reduction in potential therapeutic effectiveness of raising vascular colloid oncotic pressure in low-pressure pulmonary edema (15).

Effect of furosemide on factors governing lung liquid balance. The major factors governing the net flow of lung liquid (Q_E) from pulmonary microvessels (mv) to lung interstitium (is) may be expressed in the equation: $Q_E = Kf[(Pmv - Pis) - (\pi mv - \pi is)\sigma] - Q$ lymph, where P and π represent hydrostatic and colloid oncotic pressures, respectively, Kf is the pulmonary microvascular permeability coefficient, σ is the reflection coefficient of the capillary membrane, and Q lymph represents pulmonary lymphatic flow and any other factors removing liquid from the lung interstitium (14). Because OA did not raise Pmv as deduced from the pulmonary vascular pressures (Table I) or lower πmv as deduced from protein concentrations (Table II), the pulmonary edema is likely a result of a substantial increase in Kf, to a lesser extent to reduced σ, and remotely to altered Pis, $\pi$is, or Q lymph. Once Kf is increased and σ is reduced, the amount of edema flow is very sensitive to altered Pmv and quite insensitive to altered πmv (15).

After receiving furosemide, dogs in group OA + F tended to increase their mean Ppa (16.7–19.2 mmHg) and to decrease their Ppw (Table I). During the same time, group OA dogs had a larger and statistically significant reduction in Ppw and tended to decrease Ppa (16.3–14.5 mmHg). To the extent that the ratio of vascular resistance upstream and downstream from the site of major leak is not substantially altered by furosemide, these hemodynamic measurements indicate that Pmv increased in group OA + F compared with group OA during the 2 h after furosemide (16). Because πmv was not different between groups after furosemide (Table II), edema should increase in group OA + F. These considerations are consistent with the strong tendency of W/D of excised group OA + F lungs to exceed W/D of group OA lungs.

On the other hand, increased Pmv after furosemide goes counter to the expected change if furosemide reduced the rate of edema formation as suggested by the indicator-dilution data in Fig. 2 discussed above. Reduced edema formation might occur despite increased Pmv if furosemide reduced Kf or increased Q lymph. We are aware of no evidence concerning furosemide effects on pulmonary microvascular Kf, but the possibility is not inconsistent with effects of diuretics on water transport in other organs. Furosemide has complex effects on thoracic duct lymph flow (17, 18), but the available evidence suggests that lymph flow changes in accord with factors governing Q_E, as if furosemide were having no direct effect on lymphatic mobility (19, 20).

One explanation of reduced shunt, reduced edema, and increased Ppa after furosemide is enhanced pulmonary vasoconstriction in edematous lung regions. Such an effect of furosemide would reduce the fraction of total pulmonary blood flow going to nonventilated lung units. To the extent that such vasoconstriction was upstream from the major site of liquid leak, hydrostatic pressure there (Pmv) would tend to decrease after furosemide (21). In turn, Q_E might decrease considerably for a small reduction in Pmv because Kf is high (15). In our study, Ppa tended to increase after furosemide, and PVR, calculated as (Ppa − Ppw)/Qt, increased considerably. These hemodynamic measurements were made at end-expiration when alveolar pressure (Palv) was 0, so Ppw exceeded Palv in all lung regions in groups OA and OA + F. Accordingly, this calculation of PVR indicates narrowing of pulmonary vessels in group OA + F compared with group OA, and underestimates the narrowing to the extent

that increased Ppa in group OA + F recruits and distends pulmonary vascular bed (22). Although reduced Qt is associated with increased PVR, Qt decreased by a similar amount in groups OA and OA + F between 2 and 4 h. Furthermore, if furosemide is reducing edema, it seems likely that pulmonary vascular compression by edema is decreasing in group OA + F compared with group OA. These considerations suggest that PVR increased after furosemide in part as a result of pulmonary vasoconstriction. This vasoconstriction could reduce edema formation and shunt if it occurred predominantly upstream from the major site of leak in edematous lung regions.

We are unaware of conclusive studies of the effects of furosemide on pulmonary vascular tone in vivo. Furosemide blocks adrenergic constriction of mesenteric vessels (23), and a brief communication suggests a similar action on intralobar pulmonary veins (24). Recent studies in our laboratory demonstrated that the fraction of pulmonary blood flow perfusing a single edematous lobe in otherwise normal lungs of anaesthetized dogs increased 30 min after furosemide when the lobar edema had not changed and the lobar shunt decreased (unpublished observations). These results do not support pulmonary vasoconstriction in edematous regions as an explanation of reduced shunt after edema, but offer an alternative consistent with most of our data. Conceivably, pulmonary vascular tone is increased in lungs made edematous by OA, furosemide reduces vascular tone, and fractional perfusion increases to lung units in which alveolar flooding and vascular compression by edema is not the limiting impedance to flow. Consequent redistribution of pulmonary blood flow away from edematous lung units is associated with reduced Qs/Qt and reduced Ppa. The latter is associated with derecruitment of vessels having closing pressures, as might be imagined to occur preferentially in edematous regions where extravascular pressures (Pis) are elevated. This secondary effect would further reduce shunt and increase PVR.

Comparison of furosemide effects in high- vs. low-pressure pulmonary edema. Pulmonary edema secondary to left ventricular failure is quite responsive to furosemide. The reductions in symptoms, intrapulmonary shunt, and radiologic edema have been attributed to diuresis and the diuretic enhanced capacitance of the systemic veins. Both mechanisms reduce CBV, which in turn reduces Pmv in inverse proportion to the compliance of the pulmonary circulation. Consideration of our data in low-pressure edema focused our attention on the left ventricular diastolic compliance as the major determinant of ΔPmv. Because the left ventricular diastolic volume-pressure characteristics are nonlinear (Fig. 4), a reduction in CBV and left ventricular diastolic volume after furosemide causes a large fall in Pmv in cardiogenic pulmonary edema,

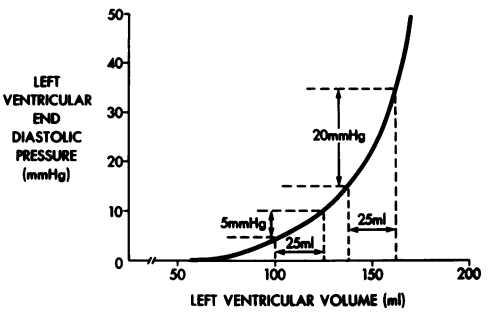

FIGURE 4 Schematic diastolic volume (abscissa) -pressure (ordinate) relationship of the left ventricle. When furosemide reduces left ventricular end diastolic volume by 25 ml, left ventricular end diastolic pressure decreased by 20 mmHg in cardiogenic edema and by 5 mmHg in low-pressure edema. For discussion, see text.

but the same reduction in ventricular volume in low-pressure pulmonary edema causes a much smaller reduction in ventricular diastolic pressure and Pmv.

Kiely et al. (5) studied the central hemodynamic effects of 40 mg of intravenous furosemide in 15 patients with acute myocardial infarction. In the nine patients who had a large diuresis, Ppw decreased from 20±4 to 12±3. In 27 patients with elevated left atrial pressures (P_{La}), furosemide or ethacrynic acid lowered mean left atrial pressure from 22 to 15 mmHg despite a small reduction in mean pulmonary blood volume from 341 to 321 ml (6). In contrast, seven patients with normal central hemodynamics during the convalescent period of high altitude pulmonary edema had a small and insignificant reduction in mean atrial pressure from 5.0 to 3.5 mmHg when furosemide caused a much larger reduction in mean pulmonary blood volume from 327 to 252 ml (3). In normal adult sheep, 80 mg of furosemide caused mean P_{La} to decrease from 2.5 to 1.2 mmHg (20). This small reduction in hydrostatic pressure was statistically significant and was associated with a 30% reduction in pulmonary lymph flow, which the investigators attributed to reduced steady-state edema formation. Similarly, Bland et al. (19) observed in eight normal lambs that P_{La} decreased from 2 to 1 mmHg ($P < 0.05$) associated with a 27% reduction in lymph flow. In five lambs given large saline loads in the same study, P_{La} increased to 9 mmHg. After furosemide, P_{La} decreased from 9 to 1 mmHg, and lymph flow was reduced to one-half of the control value. These data support the concept that furosemide has a much greater effect on Pmv in cardiogenic or high-pressure pulmonary edema than in pulmonary edema associated with low or normal vascular pressures, presumably because the left ventricular diastolic volume-pressure relationship is quite curvilinear.

Although the reduction in left ventricular diastolic pressure is much less in low-pressure edema, such

small reductions may effectively reduce the edema formation rate because Kf is so high. In this setting, Pmv and its effects on edema may be affected as much by small changes in pulmonary vascular muscle tone as by altered ventricular diastolic volume. Pulmonary venous dilatation or pulmonary arteriolar constriction by furosemide could lower the hydrostatic pressure at the leak site by several millimeters of Mercury without detectable changes in Ppa or Ppw (16). Similarly, pulmonary venous constriction or arteriolar dilation would increase Pmv and edema. These considerations suggest that even limited vasoactive effects of furosemide easily overlooked in cardiogenic edema might significantly alter low-pressure edema formation rate. This rationale applies to other pulmonary vasoactive drugs commonly used in acutely ill patients for other reasons; viz., nitroprusside, isoproterenol, and dopamine. Finally, the effects of these drugs on ventricular function and diastolic volume-pressure curves may significantly alter Pmv and edema. Apparently, furosemide has no such effects on canine left ventricular function (25).

In summary, out attempt to determine the mechanism of action of furosemide in a canine model of low-pressure pulmonary edema revealed several surprising differences from cardiogenic edema. First, pulmonary oxygen exchange was considerably improved 2 h after furosemide with only equivocal reductions in the amount of edema. Second, if the edema were reduced by furosemide, this effect could not be attributed to measured reductions in Ppw or Ppa. Accordingly, both the improved gas exchange and the reduced edema are as likely a result of the pulmonary vasoactive effects of furosemide redistributing pulmonary blood flow away from edematous areas and the lowering the hydrostatic pressure in pulmonary microvessels. Such effects are less important and unreported in cardiogenic edema, where furosemide-induced reduction in CBV causes a large reduction in Pmv, edema, and shunt because of the low diastolic compliance of the distended ischemic left ventricle.

Although furosemide produces smaller reductions in Pmv in low-pressure edema, it seems reasonable to employ this therapy because even minor reductions in Pmv markedly reduce the rate of edema formation when pulmonary capillary permeability is increased. Such an approach requires careful monitoring of some estimate of Pmv and the awareness that altered pulmonary vascular tone might confound estimates based on measured Ppa and Ppw. One approach is to use diuretics and fluid restriction to seek the lowest Ppw consistent with adequate cardiac output. An acknowledged pulmonary risk of induced circulatory hypovolemia is that it may increase the permeability per se (26). Another potential problem is that potent loop diuretics obscure the early detection of renal hypoperfusion by prerenal oliguria. Conceivably, reduced Qt and renal blood flow during circulatory hypovolemia can be prevented by vasoactive agents such as dopamine used in the dopaminergic range (3–5 μg/kg per min). Finally, when further reduction in Pmv and edema is sought after circulating blood volume and Qt are reduced to acceptable limits, agents which alter left ventricular diastolic compliance or systolic pumping function may be effective. Because each vasoactive agent employed may have significant and independent effects on pulmonary shunt and pulmonary edema formation, measured changes in Qs/Qt are only loose and indirect indicators of edema rate in pulmonary capillary leak. Further attempts to test these complicated therapeutic considerations seem warranted because current therapy of pulmonary capillary leak is associated with high mortality (27).

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