Decreased Pulmonary Transvascular Fluid Filtration in Awake Newborn Lambs after Intravenous Furosemide

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ABSTRACT We studied the effect of furosemide on pulmonary transvascular filtration of fluid and microvascular permeability to plasma proteins by measuring steady-state lung lymph flow and protein flow, pulmonary arterial and left atrial pressures in nine 1-wk-old unanesthetized lambs before and after rapid intravenous infusion of furosemide, 1 mg/kg in 10 experiments and 8 mg/kg in 5 experiments. With rapid diuresis induced by furosemide (an eightfold increase in urine flow), lung vascular pressures decreased, protein concentrations of lymph and plasma increased, and there was a consistent decrease in lymph flow and lymph protein flow, more pronounced after the larger dose. Five additional lambs received 8 mg/kg of furosemide intravenously in the presence of saline-induced pulmonary edema; in these experiments, the decrease in vascular pressures, increase in transvascular protein gradient, and decrease in lymph flow were greater than in lambs without pulmonary edema. These findings suggest that furosemide decreases transvascular filtration of fluid in the lung by diminishing the transvascular hydraulic pressure gradient and increasing the transvascular gradient for protein osmotic pressure. In five acute experiments on anesthetized lambs with kidneys removed, 8 mg/kg of intravenous furosemide decreased lymph flow one-half as much as it did in the presence of kidneys, with no change in lung vascular pressures or protein concentrations. The results of experiments in lambs without kidneys are consistent with a reduction in the vascular surface area for exchange of fluid and protein in the lung.

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INTRODUCTION

Furosemide is a potent sulfonamide diuretic which has become a mainstay in the treatment of pulmonary edema. Several investigators have attributed its benefits to reduced plasma volume and pulmonary vascular pressures that result from diuresis (1–4). Others have suggested that patients with pulmonary edema derive rapid improvement from furosemide even before diuresis, because of an extrarenal site of action (5–7), possibly related to changes in pulmonary blood volume.

Measurement of the volume of extravascular lung water by the double-indicator dilution method (8) and determination of arterial blood gas tensions (9) in patients before and after the administration of furosemide have demonstrated no significant acute changes. These methods may not be sufficiently sensitive to detect rapid but small changes in the volume and distribution of lung fluid, and may demand a longer duration of diuretic therapy to distinguish significant differences. The work of Staub and associates (10–14) showed that measurement of steady-state pulmonary lymph flow and protein flow in sheep can be used to demonstrate small changes in lung fluid dynamics.

We studied the mechanism of action of furosemide on pulmonary transvascular filtration of fluid and microvascular permeability to plasma proteins by observing the effects of the drug on steady-state lung vascular pressures, pulmonary lymph flow, and lymph protein flow in unanesthetized 7–10-day-old lambs. Furosemide decreased pulmonary vascular pressures, increased plasma protein concentration, and induced a dose-dependent decrease of lung lymph flow, consistent with a reduction of net transvascular filtration of fluid in the lung. The effect was greatest in five lambs with pulmonary edema induced by infusions of saline. In acute experiments on five lambs with kidneys

removed, lymph flow also decreased after furosemide, but to a lesser extent than in the chronic experiments, with no change in pulmonary vascular pressures or protein concentrations, thus suggesting a partial extrarenal effect on pulmonary transvascular fluid dynamics.

METHODS

Preparation of lambs. Our preparation for these experiments has been described in detail elsewhere (12, 15). We surgically prepared 14 newborn lambs (average birth wt 3.8 kg, range 2.3–5.2 kg) to isolate and collect lung lymph and measure average pulmonary arterial ($\bar{P}pa$)[1] and average left atrial ($\bar{P}la$) pressures. Each lamb had two thoracotomies, the first within 48 h after birth and the second 4–7 days later. They received anesthesia with halothane and nitrous oxide and were ventilated with a piston-type respirator (model 607, Harvard Apparatus Co., Inc., Millis, Mass.) during surgery. Before and after surgery, and between experiments, the lambs remained with their ewes for feeding and warmth.

In the first operation, we placed polyvinyl catheters in the thoracic aorta, both atria, and the pulmonary artery. After the lambs recovered, a second thoracotomy was done to obtain pulmonary lymph. In lambs, about two-thirds of the lung lymph flows into the thoracic duct by way of the caudal mediastinal lymph node (16, 17), which is a long, narrow structure located in the posterior mediastinum between the aorta and esophagus on the right side of the chest. We ligated and severed the systemic contributions to that lymph node and inserted a heparin-coated polyvinyl catheter, internal diameter 0.011 or 0.015 inches, into the efferent duct of that node for collection of nearly pure pulmonary lymph. Previous studies on adult sheep demonstrated that this fluid is not contaminated by lymph of systemic origin (12). We tunneled the catheter beneath the pleura, brought it through the chest wall, secured it to the skin with a suture, and protected it with a canvas pouch. In addition, we placed a polyvinyl catheter in the pleural space for postoperative drainage of pleural fluid and air. After surgery, the lambs had at least 2 days to recover, and experiments did not begin until the pleural cavity was free of fluid and the lymph contained no visible blood and flowed at a steady rate.

Chronic experiments. The average wt of the lambs at the time of experiments was 5.9 kg (range 4.1–7.9 kg). During experiments, we kept the lambs, without restraints, in a cardboard box. We measured $\bar{P}pa$, $\bar{P}la$, and the phasic aortic blood pressure continuously with calibrated pressure transducers (Statham P23 Dc, Statham Instruments, Inc., Oxnard, Calif.) and a four-channel amplifier-recorder (Grass model 7B polygraph, 7DAE amplifiers, and 7PlB preamplifiers, Grass Instrument Co., Quincy, Mass.). Zero reference level for all pressure measurements was a line drawn at the time of surgery on the lamb's skin at the level of the left atrium.

We measured lymph flow to the nearest 0.01 ml at 30-min intervals for 2 h during a steady-state base-line period and for 4 h after rapidly injecting furosemide (Lasix, 10 mg/ml, Hoechst-Roussel Pharmaceuticals, Somerville, N. J.) into the right atrium. We collected samples of lymph and blood in heparinized test tubes every 30 min, with blood specimens taken at the midpoint of each lymph collection period. In 10 experiments performed on eight lambs, we infused 1 mg/kg of furosemide and observed the effects on pulmonary lymph flow and hemodynamics. On separate days, five of the lambs received 8 mg/kg of furosemide after a steady-state base-line period. We collected urine either by an indwelling polyvinyl catheter in the bladder or by intermittent emptying of a plastic receptacle suspended beneath the lambs. We measured heart rate, respiratory rate, and rectal temperature, and obtained samples of arterial blood for measurement of pH and blood gas tensions at frequent intervals.

Pulmonary edema experiments. We induced pulmonary edema in five lambs, more than doubling their steady-state base-line lymph flow, by infusing sterile isotonic saline solution, 154 meq/liter, intravenously at a rate of 150–200 ml/kg per h for 3 h. We measured $\bar{P}pa$, $\bar{P}la$, protein concentrations, and lymph flow for at least 2 h after the infusion, sufficiently long to permit equilibration, and then during a 2-h period after the injection into the right atrium of furosemide, 8 mg/kg.

Acute experiments in lambs without kidneys. In five lambs less than 2-wk-old that weighed an average of 7.0 kg (range 5.4–10.0 kg), we did bilateral thoracotomies as previously described, in addition to bilateral nephrectomies (without adrenalectomy), and then measured steady-state lymph flow and vascular pressures under anesthesia with halothane and nitrous oxide for 2 h before and 4 h after 8 mg/kg of intravenous furosemide. Except for the anesthesia and mechanical ventilation, the experiments were almost identical in design to the chronic studies. We killed the lambs 4 h after the infusion of furosemide. We measured vascular pressures and lymph flow for 6–8 h in two anesthetized, anephric control lambs, given no furosemide.

Post-mortem studies. At the conclusion of experiments on each animal, we injected pentobarbital sodium, 20 mg/kg, into the right atrium, placed the lamb in the supine position, ventilated the lungs with 20 ml/kg of air via the Harvard respirator (Harvard Apparatus, Co., Inc.), and rapidly split the sternum to excise both lungs. We clamped the hili of the lungs at end-inspiration with the heart still beating, and removed the lungs for measurement of extravascular water and dry lung tissue weight. We did this with six lambs under base line conditions (no furosemide) (15), with six lambs 4 h after they received 1 mg/kg of furosemide, and with five anephric lambs 4 h after they received 8 mg/kg of furosemide.

Analytic methods. We centrifuged samples of lymph and blood and measured the concentration of protein in the supernates by the Biuret method (18), and albumin and globulin fractions by cellulose-acetate electrophoresis (Microzone 110, Beckman Instruments, Inc., Fullerton, Calif.). We measured arterial blood gas tensions on a blood-gas analyzer (Acid-Base Analyzer PHM 71, Radiometer Co., Copenhagen, Denmark) with calibration at 40°C, the normal body temperature of lambs.

We calculated the weight of extravascular lung water per gram of dry lung tissue, exclusive of blood, for all lambs by a modification (11, 13) of the method described by Pearce et al. (19). We expressed pulmonary lymph flow and protein flow (lymph flow × lymph protein concentration) relative to the weight of dry bloodless lung tissue. In addition, we expressed protein flow in relation to the concentration of protein in the plasma of each animal.

Statistics. We compared average steady-state measurements made before and after infusion of furosemide for each experiment, with the paired t test for statistical analysis (20). We accepted $P < 0.05$ as indicative of significant differences. Post-mortem lung water measurements made after base-line experiments and furosemide experiments were compared by the unpaired t test. All summary results in both the text and the tables are expressed as the mean ± 1 SEM.

[1] *Abbreviations used in this paper*: $\bar{P}la$, average left atrial pressure; $\bar{P}pa$, average pulmonary arterial pressure.

RESULTS

1-mg/kg experiments. Fig. 1 illustrates the results of a typical study in which a lamb received 1 mg/kg of furosemide after a 2-h base-line period. Associated with the ensuing diuresis, $\bar{P}pa$ and $\bar{P}la$ decreased, but only slightly, phasic aortic blood pressure did not change, protein concentrations and hematocrit increased, and lung lymph flow diminished.

Table I lists the important data related to pulmonary transvascular fluid filtration and microvascular permeability to plasma proteins for 10 such experiments carried out on eight lambs. $\bar{P}pa$ did not change significantly; there was a small but significant decrease in $\bar{P}la$, an increase in lymph (12%) and plasma (8%) protein concentrations, and a 28% decrease in lymph flow, with diminished protein flow as well. There was no consistent change in the lymph concentration of total protein relative to that in plasma after furosemide.

Urine flow increased abruptly from 3±1 ml/kg per h during the base-line period to 24±4 ml/kg per h during the 2 h after furosemide. In lambs with catheters in the bladder, we detected a substantial increase in urine flow within 5 min of the furosemide infusion, reaching a maximal flow rate between 15 and 45 min after the drug.

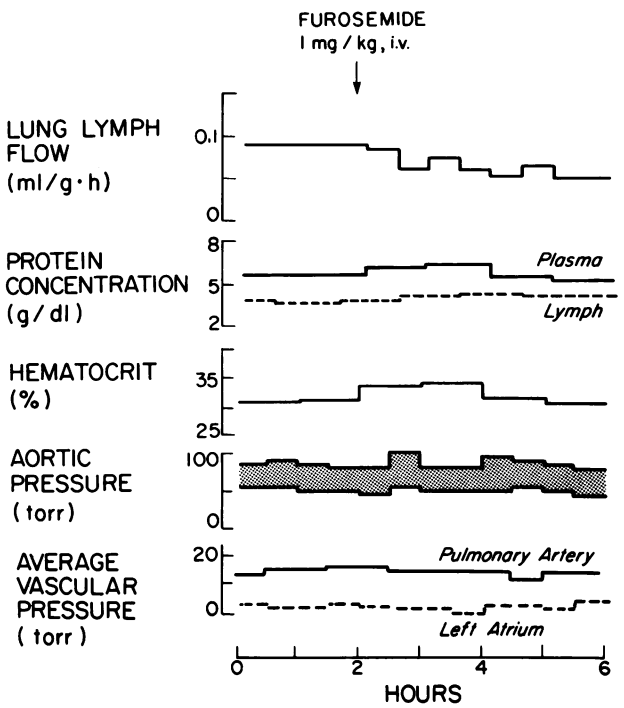

FIGURE 1 Effect of intravenous furosemide, 1 mg/kg, on steady-state lung lymph flow (per gram of dry lung tissue, exclusive of blood), protein concentrations, hematocrit, and vascular pressures in an unanesthetized lamb.

The average hematocrit increased from 27±1 to 29±1. Neither the phasic aortic blood pressure (88±3/53±2 torr to 87±3/52±2 torr) nor the heart rate (189±4/min to 193±5/min) changed significantly, but respiratory frequency did decrease from 86±7/min to 69±4/min, with a significant decline in the average CO_2 pressure in arterial blood from 39±2 torr to 37±1 torr and an increase in pH from 7.41±0.01 to 7.43±0.03. There was no significant change in O_2 pressure in arterial blood (79±4 torr to 79±3 torr) after furosemide.

8-mg/kg experiments. Fig. 2 shows the results of a typical experiment in which a lamb received 8 mg/kg of furosemide. With the higher dose, there was a more striking response in pulmonary transvascular fluid filtration, demonstrated by the substantial decrease in lymph flow. Again, protein concentrations increased, as did the hematocrit, and lung vascular pressures lessened, but only slightly.

Table II lists the results of five such studies. $\bar{P}pa$ decreased in all experiments, while $\bar{P}la$ did so in three and was unchanged in two. Protein concentrations increased more than in the 1-mg/kg experiments, and there was a 39% decrease in lung lymph flow, with a 36% reduction in protein flow. In four of the five experiments, the protein concentration in lymph increased in relation to that in plasma, consistent with a decrease in the pulmonary transvascular hydraulic pressure gradient.

Urine output increased from 4±0.3 ml/kg per h to 33±4 ml/kg per h after furosemide, and average hematocrit increased from 27±0.3 to 30±1%. As with the lower dose, there was no significant change in heart rate, systolic blood pressure, or O_2 pressure in arterial blood, but diastolic blood pressure in the aorta declined (by an average decrement of seven torr) in all five experiments; CO_2 pressure in arterial blood decreased and pH increased in four studies.

Pulmonary edema experiments. Fig. 3 illustrates a typical experiment in which we infused isotonic saline intravenously at a rate of 165 ml/kg per h for 3 h to induce pulmonary edema, allowed 2–3 h for a "quasi-steady state" to develop, and then injected furosemide, 8 mg/kg, into the right atrium. Lymph flow decreased abruptly, though $\bar{P}pa$ and $\bar{P}la$ remained unchanged for more than 30 min, after which they decreased. While plasma protein concentration increased soon after the injection of furosemide, lymph protein concentration did not increase for more than 1 h, thereby augmenting the transvascular gradient for protein. Table III lists data related to pulmonary hemodynamics, transvascular fluid and protein transport, and arterial blood gas tensions for the five lambs given furosemide during saline-induced pulmonary edema. In all cases, $\bar{P}pa$ and $\bar{P}la$ decreased, plasma protein concentration increased, and lymph flow and protein flow decreased. Associated

TABLE I

Pulmonary Hemodynamics and Fluid and Protein Transport in Eight Awake 7–10-Day-Old Lambs before and after Intravenous Furosemide, 1 mg/kg

Lamb	Weight		Time relative to furosemide infusion	Vascular pressures		Protein concentrations				Lymph flow	Protein flow
						Lymph		Plasma			
	Body	Dry bloodless lung		P̄pa	P̄la	Total	% Alb*	Total	% Alb*		
	kg	*g*		*torr*		*g/dl*		*g/dl*		*ml/h·g‡*	*mg/h·g·g‖§*
1	7.9	26.8	Before	15	3	3.87	45	5.34	36	0.10	0.70
			After	16	2	4.34	44	5.62	38	0.07	0.53
2	4.3	12.0	Before	19	4	2.92	41	5.17	38	0.12	0.68
			After	21	1	3.52	40	5.64	37	0.10	0.63
	4.2	12.0	Before	18	0	3.38	48	5.54	35	0.09	0.54
			After	18	0	2.57	50	5.44	38	0.07	0.34
3	4.5	12.6	Before	23	1	2.30	49	4.61	37	0.19	0.95
			After	20	0	2.92	48	5.03	40	0.14	0.81
4	6.4	23.9	Before	13	0	3.55	49	4.72	39	0.04	0.28
			After	12	−1	3.87	47	5.40	41	0.03	0.23
5	7.8	35.8	Before	19	1	3.18	50	5.41	38	0.08	0.45
			After	19	1	3.32	49	5.61	38	0.07	0.43
	7.6	35.8	Before	19	3	2.77	52	5.35	39	0.08	0.41
			After	17	0	3.37	51	5.93	40	0.04	0.24
6	5.7	19.6	Before	22	5	2.78	52	4.88	39	0.14	0.79
			After	20	3	3.16	55	5.39	38	0.07	0.38
7	6.1	18.5	Before	16	2	2.78	55	4.41	39	0.13	0.83
			After	15	1	2.98	43	4.81	40	0.12	0.73
8	6.8	33.9	Before	17	3	2.51	46	4.63	34	0.14	0.75
			After	15	1	3.43	41	5.01	32	0.09	0.59
Mean±SEM	6.1±0.5	22.9±3.2	Before	18±1	2±0.5	3.00±0.15	49±1	5.01±0.13	37±1	0.11±0.01	0.64±0.07
			After	17±1	1±0.6	3.35±0.16	47±2	5.39±0.11	38±1	0.08±0.01	0.49±0.06
P				NS	<0.05	<0.05	NS	<0.05	NS	<0.05	<0.05

* Percent of total protein concentration which is albumin.

‡ Lymph flow relative to dry bloodless lung tissue.

§ Protein flow (lymph flow × lymph protein concentration) relative to dry bloodless lung tissue and plasma protein concentration.

with these changes, respiratory frequency and CO_2 pressure in arterial blood decreased, and pH and O_2 pressure in arterial blood increased. It is notable that after furosemide the concentration of protein in lymph did not increase consistently, as the plasma concentration did, when pulmonary edema was present, thereby confirming the presence of excessive interstitial fluid which continued to dilute the protein concentration in the lymph for several hours (21).

Table IV lists estimated pulmonary microvascular pressures (calculated as $\bar{P}mv = \bar{P}la + 0.4\ [\bar{P}pa - \bar{P}la]$, based on studies of Gaar et al., [22]) and protein osmotic pressures, derived from measurements of albumin and globulin concentrations applied to the curves of Landis and Pappenheimer (23). In all five lambs, estimated pulmonary microvascular pressures decreased and the transvascular gradient for protein osmotic pressure increased.

Acute experiments. Fig. 4 shows the results of an experiment in which a lamb without kidneys received 8 mg/kg of furosemide. Lymph flow decreased, with no change in vascular pressures or protein concentrations.

Table V lists the results of five such studies performed on anesthetized lambs without kidneys. Despite the fact that P̄pa, P̄la, and protein concentrations did not change, lymph flow decreased by an average of 17% after 8 mg/kg of furosemide. This observation was consistent in all five experiments and differed from two control experiments in which we studied lambs without kidneys for up to 8 h without giving furosemide, and found no decrease in lymph flow.

Post-mortem studies. Extravascular lung water

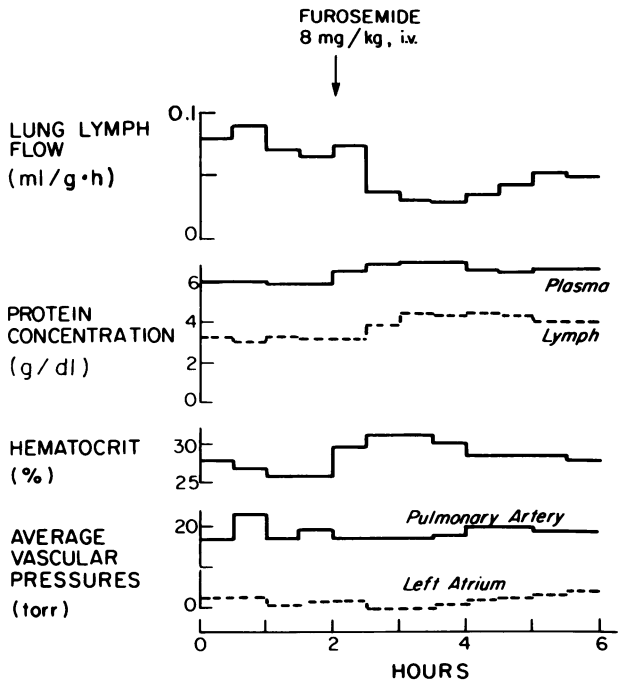

FIGURE 2 Effect of intravenous furosemide, 8 mg/kg, on steady-state lung lymph flow (per gram of dry lung tissue, exclusive of blood), protein concentrations, and vascular pressures in an unanesthetized lamb.

averaged 4.80±0.19 g/g of dry lung tissue, exclusive of blood, in lambs given 1 mg/kg of furosemide 4 h before death, compared to 4.82±0.11 g/g of dry bloodless lung in control animals. These results do not differ significantly, nor are they different from the 4.62±0.09 g of extravascular lung water/g of dry lung tissue measured in anephric lambs given 8 mg/kg of furosemide during anesthesia.

DISCUSSION

Furosemide has been used to treat pulmonary edema for more than a decade, yet its action on fluid dynamics within the lung has been inaccessible without a sensitive method for detecting small changes in the net transvascular flow of fluid. The technique of Staub and his associates (10–14) has permitted us to examine more closely the changes in liquid movement which occur in the lung after furosemide. Our results suggest that it reduces transvascular filtration of fluid in the lung, more so after 8 mg/kg than after 1 mg/kg; the effect was most pronounced in the presence of pulmonary edema. Estimates of pulmonary microvascular pressures and protein osmotic pressures suggest that the changes in lymph flow reflect both a decrease in the pulmonary transvascular hydraulic pressure gradient and an in-

TABLE II

Pulmonary Hemodynamics and Fluid and Protein Transport in Five Awake 7–10-Day-Old Lambs before and after Intravenous Furosemide, 8 mg/kg

	Weight		Time relative to furosemide infusion	Vascular pressures		Protein concentrations					
						Lymph		Plasma			
Lamb	Body	Dry bloodless lung		$\bar{P}pa$	$\bar{P}la$	$\frac{g}{d}$	% Alb*	Total	% Alb*	Lymph flow	Protein flow
	kg	*g*		Total		*g/dl*		*g/dl*		*ml/h·g*‡	*mg/h·g·g*$_p$§
5	7.7	35.8	Before	19	2	3.29	53	5.80	39	0.07	0.38
			After	18	−1	4.11	50	6.56	37	0.03	0.18
6	5.7	19.6	Before	20	5	2.71	56	4.77	41	0.10	0.59
			After	18	3	3.03	52	5.48	39	0.05	0.26
7	6.4	18.5	Before	22	3	2.62	47	4.63	37	0.12	0.70
			After	19	3	3.13	48	5.18	33	0.09	0.53
8	5.8	33.9	Before	17	2	2.98	50	5.36	38	0.13	0.70
			After	16	−1	3.60	49	5.76	37	0.08	0.52
9	6.7	19.4	Before	20	6	2.40	49	4.85	41	0.22	1.11
			After	17	6	2.70	49	5.47	39	0.15	0.75
Mean±SEM	6.5±0.4	25.4±3.9	Before	20±1	4±1	2.80±0.15	51±2	5.08±0.22	39±1	0.13±0.03	0.70±0.12
			After	18±1	2±1	3.31±0.25	50±1	5.69±0.24	37±1	0.08±0.02	0.45±0.10
P				<0.05	NS	<0.05	NS	<0.05	<0.05	<0.05	<0.05

* Percent of total protein concentration which is albumin.

‡ Lymph flow relative to dry bloodless lung tissue.

§ Protein flow (lymph flow × lymph protein concentration) relative to dry bloodless lung tissue and plasma protein concentration.

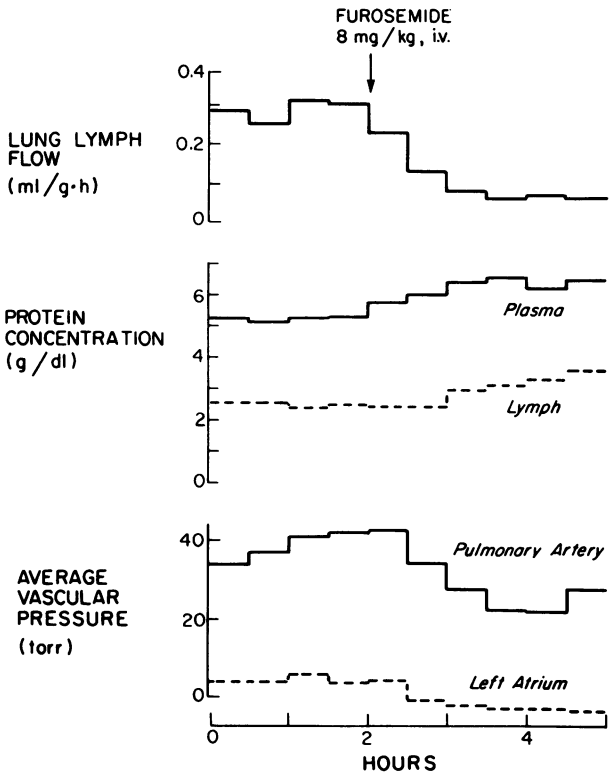

FIGURE 3 Effect of intravenous furosemide, 8 mg/kg, on steady-state lung lymph flow (per gram of dry lung tissue, exclusive of blood), protein concentrations, and vascular pressures in an unanesthetized lamb with pulmonary edema which had been induced by an infusion of isotonic saline, 165 ml/kg per h, for 3 h.

crease in the transvascular gradient for protein osmotic pressure. In addition, the drug appears to have a partial effect even in the absence of kidneys, without any change in lung vascular pressures or protein concentrations.

Despite the fact that lymph flow in lambs decreased after infusion of furosemide, extravascular lung water was not significantly different for lambs killed 4 h after receiving the diuretic compared to lambs killed after no diuretic. This finding confirms the observations of Brigham et al. (11) and Erdmann et al. (13) that in sheep measurement of pulmonary lymph flow is a more sensitive index of transvascular fluid filtration than measurement of extravascular lung water.

Lal et al. (1) found no significant change in $\bar{P}pa$ or $\bar{P}la$ after furosemide in human patients with an initial $\bar{P}la$ less than 10 torr; when $\bar{P}la$ was above 10 torr however, furosemide caused a significant decrease in $\bar{P}pa$ and $\bar{P}la$. Decreases of $\bar{P}pa$ and $\bar{P}la$ were small and inconsistent in our base-line experiments, perhaps because these were normal lambs; the changes were more evident in lambs with pulmonary edema from circulatory overload. Under these circumstances, furosemide not only reduced filtration pressure in the lung, but also induced significant improvement of arterial blood gas tensions, presumably from enhanced clearance of excessive interstitial and perhaps some alveolar fluid.

While many investigators have directed their interest to effects of furosemide on pulmonary vascular pressures (1–4, 8, 24, 25), the influence of the drug on the transvascular protein osmotic pressure gradient has re-

TABLE III

Pulmonary Hemodynamics and Fluid and Protein Transport in Five Lambs with Saline-Induced Pulmonary Edema, before and after Intravenous Furosemide, 8 mg/kg

Lamb	Weight		Conditions	Vascular pressures		Total protein concentration		Lymph flow	Protein flow	Arterial blood		
	Body	Dry bloodless lung		$\bar{P}pa$	$\bar{P}la$	Lymph	Plasma			pH	O_2 pressure	CO_2 pressure
	kg	*g*		*torr*		*g/dl*		*ml/h·g**	*ml/h·g·g$_p$‡*		*torr*	
10	6.4	21.4	Pulmonary edema	31	12	1.20	4.34	0.33	0.91	7.19	38	60
			After furosemide	20	2	0.93	5.83	0.20	0.32	7.38	57	44
11	6.3	19.3	Pulmonary edema	34	10	1.65	4.93	0.39	1.31	7.18	53	59
			After furosemide	22	4	1.90	5.55	0.16	0.55	7.32	67	44
12	5.7	22.5	Pulmonary edema	39	5	2.52	5.22	0.29	1.40	7.22	51	60
			After furosemide	25	−3	3.24	6.40	0.07	0.35	7.37	59	54
13	4.3	20.0	Pulmonary edema	38	9	1.86	3.70	0.23	1.16	7.10	51	49
			After furosemide	26	1	1.73	4.43	0.17	0.66	7.23	53	48
14	4.1	14.7	Pulmonary edema	32	8	0.99	4.66	0.47	1.00	7.09	47	53
			After furosemide	20	2	1.06	5.80	0.26	0.48	7.33	78	43
Mean±SEM	5.4±0.5	19.6±1.3	Pulmonary edema	35±2	9±1	1.64±0.27	4.57±0.26	0.34±0.04	1.16±0.09	7.16±0.03	48±3	56±2
			After furosemide	22±1	1±1	1.77±0.41	5.60±0.32	0.17±0.03	0.47±0.06	7.33±0.03	57±3	47±2
P				<0.05	<0.05	NS	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

* Lymph flow relative to gram of dry bloodless lung tissue.

‡ Protein flow relative to gram of dry bloodless lung tissue and plasma protein concentration.

TABLE IV

Derived Data for Pulmonary Microvascular Pressure and Protein Osmotic Pressures of Lymph and Plasma in Lambs with Saline-Induced Pulmonary Edema Treated with Intravenous Furosemide, 8 mg/kg

Lamb	Conditions	Pulmonary microvascular pressure	Protein osmotic pressure*		
		$\bar{P}la + 0.4 (\bar{P}pa - \bar{P}la)$ (22)	Lymph	Plasma	Transvascular gradient‡
		torr		*torr*	
10	Pulmonary edema	19	2.8	11.0	8.2
	After furosemide	9	2.1	15.5	13.4
11	Pulmonary edema	20	3.9	12.7	8.8
	After furosemide	11	4.5	14.7	10.2
12	Pulmonary edema	18	6.2	14.1	7.9
	After furosemide	8	8.3	18.1	9.8
13	Pulmonary edema	21	4.4	9.0	4.6
	After furosemide	11	4.1	11.1	7.0
14	Pulmonary edema	18	2.5	12.4	9.9
	After furosemide	9	2.7	15.9	13.2
Mean±SEM	Pulmonary edema	19±1	4.0±0.7	11.8±0.9	7.9±0.9
	After furosemide	10±1	4.3±1.1	15.1±1.1	10.7±1.2
P		<0.05	NS	<0.05	<0.05

* Derived from the curves of Landis and Pappenheimer (23), based on actual measurements of fractional protein concentrations.

‡ The difference in protein osmotic pressure between plasma and lymph.

ceived less attention. In assuming that the protein concentration of lymph equals that of pulmonary interstitial fluid, a premise supported by the recent studies of Nicolaysen et al. (26) and Vreim et al. (27), our calculations for protein osmotic pressures in lambs with pulmonary edema, shown in Table IV, suggest that furosemide increases the transvascular gradient, a change which would be expected to decrease fluid filtration, hasten reabsorption of excessive interstitial fluid, and thereby diminish lymph flow. Based on our extimates of pulmonary microvascular pressure and protein osmotic pressure gradients, the latter accounted for about one-quarter of the total change in transvascular forces affecting fluid movement in lambs with pulmonary edema given furosemide.

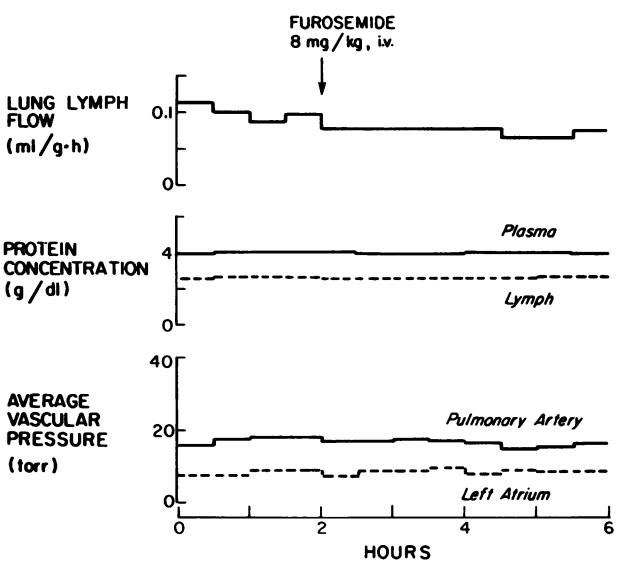

FIGURE 4 Effect of intravenous furosemide, 8 mg/kg, on steady-state lung lymph flow (per gram of dry lung tissue, exclusive of blood), protein concentrations, and vascular pressures in a lamb under anesthesia after bilateral nephrectomy.

The cause for decreased lymph flow after furosemide in the absence of kidneys remains uncertain. Dikshit et al. (7) suggested that furosemide may increase systemic venous capacitance and thereby reduce the load on the heart even before diuresis, but more recent work by Hesse et al. (4) demonstrated no change in venous tone after furosemide. Szwed et al. (28) showed that furosemide increased nonpulmonary lymph flow through the thoracic duct in dogs with or without kidneys, despite no significant change in systemic arterial or venous pressures. They concluded that furosemide produces shifts in body water by an undefined extrarenal action. Stowe and Hook (29) found that lymph flow from the kidney of anesthetized dogs is a function of renal blood flow, which increases after furosemide; that is, renal lymph flow increases with increased blood flow to the kidneys

TABLE V

Pulmonary Hemodynamics and Fluid and Protein Transport in Five Anephric, Anesthetized 1–2-Wk-Old Lambs before and after Intravenous Furosemide, 8 mg/kg

Lamb	Weight		Time relative to furosemide infusion	Vascular pressures		Protein concentrations				Lymph flow	Protein flow
						Lymph		Plasma			
	Body	Dry bloodless lung		P̄pa	P̄la	Total	% Alb*	Total	% Alb*		
	kg	*g*		*torr*		*g/dl*		*g/dl*		*ml/h·g*‡	*mg/h·g·g*$_p$§
15	7.3	19.7	Before	17	7	2.90	55	3.90	49	0.11	0.79
			After	17	7	2.83	55	4.04	47	0.09	0.63
16	6.9	18.9	Before	17	8	2.70	48	4.01	45	0.10	0.66
			After	17	9	2.57	53	3.96	44	0.08	0.51
17	5.4	18.0	Before	21	7	2.40	50	4.03	47	0.10	0.62
			After	21	7	2.60	46	4.19	43	0.08	0.49
18	10.0	24.6	Before	25	−1	2.14	55	3.78	47	0.12	0.65
			After	27	1	2.26	54	3.92	48	0.11	0.62
19	5.2	15.5	Before	21	3	1.95	64	3.78	52	0.17	0.88
			After	21	3	1.91	65	3.76	52	0.15	0.77
Mean±SEM	7.0±0.9	19.3±1.5	Before	20±1	5±2	2.42±0.17	54±3	3.90±0.05	48±1	0.12±0.01	0.72±0.05
			After	21±2	5±1	2.43±0.16	55±3	3.97±0.07	47±2	0.10±0.01	0.60±0.05
P				NS	NS	NS	NS	NS	NS	< 0.05	<0.05

* Percent of total protein concentration which is albumin.

‡ Lymph flow relative to dry bloodless lung tissue.

§ Protein flow (lymph flow × lymph protein concentration) relative to dry bloodless lung tissue and plasma protein concentration.

induced by furosemide. But how might that observation relate to pulmonary lymph flow after furosemide?

While we did not measure cardiac output in our experiments, others have found that it decreases after furosemide (1–4, 6, 8, 24), even in the absence of kidneys (25). Bourland et al. (25) recently reported that even after nephrectomy, dogs had an unexplained, significant decrease in cardiac index, with no change in pulmonary arterial or pulmonary arterial wedge pressures. If this were also true in lambs, then furosemide could decrease pulmonary lymph flow by decreasing blood flow to the lungs, thereby reducing filtration pressure; or in the absence of kidneys, where there is no change in vascular pressures, it might reduce pulmonary blood volume and limit the vascular surface area for exchange of fluid and solute, thereby decreasing lymph flow. This hypothesis is consistent with our findings in anephric lambs.

Alternatively, furosemide could lessen microvascular permeability to protein, a possibility which we cannot exclude with our results. However, the fact that the concentration of albumin relative to globulin in lymph did not increase after furosemide makes this possibility unlikely, as decreased permeability implies a change in the sieving properties of the microvascular membrane, such that we would expect greater restriction of proteins of large molecular weight. It is possible, nevertheless, that our protein fractionation method is not sufficiently sensitive to detect such changes.

Is it possible that furosemide inhibits lymphatic motility and thereby reduces pulmonary lymph flow in the absence of diuresis? The fact that lung water content did not increase with the decrease in lymph flow caused by furosemide is strong evidence that the drug does not inhibit lymph propulsion, but that it merely reduces transvascular fluid filtration. The finding of increased lymph flow through renal hilar channels (29) and the thoracic duct (28) after furosemide is further evidence that the drug is not a lymphatic depressant.

From our observations of lambs with kidneys, we conclude that a major action of furosemide is its diuretic effect, which decreases lung vascular hydraulic pressure, increases the transvascular gradient for protein osmotic pressure, and thereby diminishes the net transvascular filtration of fluid in the lung. Our results suggest that this effect is dose-related and most evident during pulmonary edema.

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