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**Research Article**

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# The Pulmonary Vasopressor Response to Decreases in Blood pH in Intact Dogs

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**ABSTRACT** The pulmonary vasopressor response to acidemia was studied in intact dogs in a hemodynamically separated lobe which was pump perfused with systemic arterial or venous blood at a fixed rate. The magnitudes of the lobar vasopressor responses to perfusion with blood rendered acidic by infusions of hydrochloric, lactic, and acetic acids, and by hypercapnia (membrane oxygenator) were significantly different. Although the PH of the perfusing blood in each group fell to similar extents (pH 7.1–7.0), the lobar pressor response was greatest with hydrochloric acid (HCl), smaller with lactic and acetic acids, and absent with hypercapnia. A lobar vasopressor response also occurred during lobar perfusion with blood which had been extracorporeally acidified with HCl or acetic acid, but then returned to control pH by infusions of sodium bicarbonate and Tris before reaching the lung. A lobar vasopressor response also resulted from pump perfusion of the lobar artery with femoral venous blood during perfusion of the isolated ipsilateral femoral artery with similarly treated aortic blood. However, no lobar vasopressor response resulted from pump perfusion of the lobar artery with blood removed transeptally from a right pulmonary vein during acidification (HCl) of the right pulmonary artery (to pH 7.0).

The data indicate that, in this experimental preparation involving closed-chest dogs spontaneously breathing air or 35% oxygen, the lobar vasopressor response to infusions of acidifying agents is not directly related to the pH of blood actually perfusing the lobar vessels. Additionally, the vasopressor response is prevented by prior perfusion of the acidified blood through a pulmo-

nary vascular bed but not by prior perfusion through the femoral vascular bed. Although these experiments do not establish the mediation of the lobar vasopressor response, activation of vasoactive agents in blood at or near the acidification site is suggested.

In these experiments, the acidemia was produced under conditions which are not like the usual ones of developing metabolic acidosis or alveolar hypercapnia, in that strong acids were directly infused into blood which perfused only one lung lobe. The mediation of the present pressor responses and of those found in the more usual forms of experimental and clinical acidosis may therefore be dissimilar.

## INTRODUCTION

Previous experiments (1–9) have shown that decreasing the pH of systemic arterial and venous blood by intravenous infusion of hydrochloric or lactic acid or by ventilatory hypercapnia at normal or high levels of systemic arterial  $P_{O_2}$ <sup>1</sup> increases pulmonary arterial pressure. In intact dogs without hypoxia, a consistent relationship has been found between the pulmonary arterial pressor response and the decrease in systemic arterial blood pH, regardless of the acidifying agents, including ventilatory hypercapnia (1). This pressor response appears to result from pulmonary vasoconstriction and to be directly related to the increase in hydrogen ion concentration of the blood perfusing the lung, and not to the accompanying increase in anion concentration. Moreover, studies in man (4, 8) as well as in intact animals (9) and in excised perfused lungs (6, 7, 10) have shown that this pressor response to acidemia is augmented by hypoxemia.

<sup>1</sup> Abbreviations used in this paper:  $P_{2D}$ , pressure transducers;  $PCO_2$ , pressure of carbon dioxide;  $PO_2$ , oxygen pressure; EHNAT, blood which has been acidified and then returned to control pH during extra corporeal circulation.

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The vasopressor response of excised lobes of dog lung to acidemia may be attenuated or abolished by ventilating the lobe with air or 95% oxygen (10). Still, other studies in intact dogs have not demonstrated a greater vascular response to decreasing blood pH during ventilation with hypoxic gases (1); and, in open-chest cats, the augmentation of the pulmonary arterial pressor response to acidemia produced by hypoxia was not greater than the pressor response to hypoxia with normal pH (7). Moreover, in patients with chronic pulmonary disease, others have not found a pulmonary vasopressor response to increasing hydrogen ion concentration of systemic arterial blood with HCl infusions (11). The pulmonary arterial pressure response to relatively mild acidemia from ventilatory hypercapnia in man may result from an increased cardiac output rather than from pulmonary vasoconstriction (12). Studies in dogs without hypoxia have usually shown that the acidemia produced by ventilatory hypercapnia constricts the pulmonary vessels (1-3, 6, 9, 13) although pulmonary vasodilation has occasionally been encountered (14). However, in excised lung lobes, ventilated with air or higher oxygen mixtures, a lobar arterial pressor response to perfusion with hypercapnic blood has been less regularly observed; divergent responses may be largely related to the nature of the perfusate (15).

The present experiments were designed to further study the pulmonary vasopressor response to decreasing blood pH in intact-chest dogs without hypoxia. A cardiac catheterization technique was employed, permitting measurements of the vasopressor response in a hemodynamically separated lobe which was pump perfused at a fixed rate with blood rendered acidic after being withdrawn from the aorta or right atrium. The circulatory and respiratory changes that accompany thoracotomy and cannulation of the pulmonary vessels were thereby avoided. The magnitudes of the lobar vasopressor responses to decreasing the pH of the pump-perfused blood by introduction of various acidifying agents into the extracorporeal circuit were compared. We also assessed the effect on the lobar vasopressor response to acidifying agents of returning the pH of acidified blood to control values extracorporeally before it perfused the lung lobe. The effects on the lobar vasopressor response of initially perfusing the acidified blood through a systemic vascular bed and through the contralateral pulmonary vascular bed before perfusion of the separated lobe were also compared in other intact-chest experiments. In other experiments in which the separated lobar artery of intact-chest dogs was perfused with dextran, the vasopressor response to lowering the pH of this perfusate was compared to that observed during perfusion with acidified blood. These studies afford additional observations on the pulmonary vasopressor response to in-

fusions of acidifying agents and suggest possible mechanisms which may contribute to the mediation of this response.

## METHODS

108 mongrel dogs (19.1-21.8 kg) were lightly anesthetized with urethane (1.0 g/kg) intravenously, and were strapped in a supine position to a fluoroscopic table. They spontaneously breathed room air or 35% oxygen through an endotracheal tube. A yellow Kifa catheter<sup>2</sup> with four side holes near the tip was passed through the atrial septum and was positioned in a large pulmonary vein from the left lower lobe. A semirigid polyvinyl catheter,<sup>3</sup> 0.9 mm o.d. and having two side holes near the tip was passed through the Kifa catheter, and wedged into a small pulmonary vein in the left lower lobe of the lung. The polyvinyl catheter was then withdrawn, 3-4 cm from the wedge position, until pressure at the tip fell abruptly, and was fixed in that position with a Cope adaptor.<sup>4</sup> Special precautions were used to ensure that measurements were made in veins of 2.0-2.5 mm in diameter without wedging. A description of this technique has been previously reported (16, 17). Another yellow Kifa catheter with four-side holes near the tip was similarly passed into the left atrium. Teflon catheters, 1.0 mm o.d. with two side holes and closed ends, were then introduced into the main pulmonary artery just beyond the pulmonary valve, into the right atrium, into a systemic artery and into the pleural space without pneumothorax. Pressures were recorded by Statham P23D pressure transducers<sup>5</sup> connected to an oscilloscopic recorder.<sup>6</sup>

A specially designed single or double lumen 20F balloon catheter<sup>7</sup> was introduced fluoroscopically from the external jugular vein into the lower lobe branch of the left pulmonary artery (Fig. 1). Pressures in the lobar artery were measured through a second lumen in this catheter, 1 to 2 cm distal to the balloon, or through a second teflon catheter which had been introduced from a peripheral vein and passed into the lobar artery 2-3 cm distal to the balloon. After all catheters were positioned, the balloon was distended with 2-4 ml of sodium diatrizoate (50%) until the pressures in the lobar artery and lobar small vein decreased to within 1-3 mm Hg of the left atrial pressure level. A Sarns<sup>8</sup> roller pump calibrated with an electromagnetic flow meter<sup>6</sup> and with a graduated cylinder was used to deliver blood to the lobar artery from the aorta through a femoral arterial catheter, or from the right atrium through a femoral venous catheter. The temperature of the extracorporeal blood was maintained at 37°C with a constant temperature control regulator.<sup>9</sup> The perfusion rate was slowly increased until mean pressure in the lobar artery distal to the balloon approximated the mean pressure in the main pulmonary artery prior to balloon distention. This flow, which varied with the balloon position, ranged from 12 to 20 ml/kg per min. (Flow rates of 25-50 ml/kg per min were used in an initial study in six dogs. Intralobar infusions of 0.3 M HCl at

<sup>2</sup> Odman-Ledin, No. 17, 887 Shick X-ray, Chicago, Ill.

<sup>3</sup> Becton-Dickerson & Co., Rutherford, N. J. No. 2VSD20.

<sup>4</sup> Becton-Dickerson & Co., Rutherford, N. J.

<sup>5</sup> Statham Physiological Div., Oxnard, Calif.

<sup>6</sup> Electronics for Medicine, White Plains, N. Y.

<sup>7</sup> U. S. Catheter & Instrument Co., Glens Falls, N. Y.

<sup>8</sup> Model 4600, Sarns, Inc., Ann Arbor, Mich.

<sup>9</sup> Lauda Temperature Regulator, Model 27-59-510-3, Brinkman Instrument Co., Westbury, N. J.

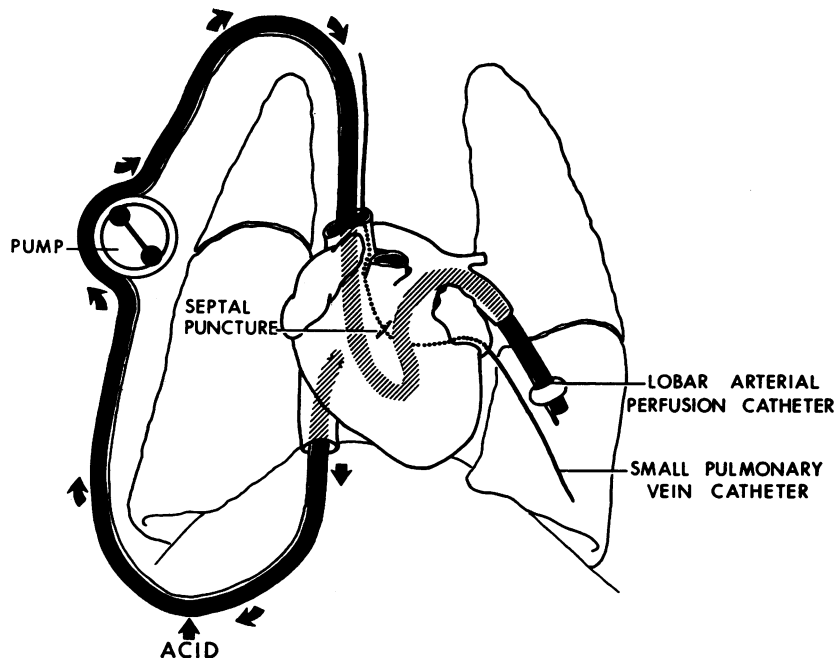


FIGURE 1 Diagram of closed-chest preparation. Diagrammatic representation of the catheter positions in the closed-chest preparation used to study pressure responses in the left lower lobe, which could be pump-perfused with right atrial blood (as shown), aortic blood via retrograde femoral arterial cannulation, pulmonary venous blood via a catheter positioned transeptally in a right pulmonary vein, or femoral venous blood. Acid-buffer was infused extracorporeally at appropriate sites.

3.82 ml/min for 4 min increased lobar arterial pressure above 60–75 mm Hg and caused evidence of gross edema in three of the perfused lobes. Data from these initial six studies are excluded from this report.) Perfusion at this constant rate was maintained for 15–20 min before control measurements were obtained. Blood samples were then withdrawn from a systemic artery, the lobar artery distal to the perfusing catheter, and from the main pulmonary artery, and were analyzed for pH,  $P_{CO_2}$ , and  $P_{O_2}$  using an ultramicro pH and blood gas analyzing system.<sup>10</sup> In experiments with acid infusions, blood removed from the perfused lobar vein was similarly analyzed. Blood flow through the normally perfused lobes, and blood volume in the pump-perfused and normally perfused lobes were measured by dye dilution techniques with the method of successive injections (18). Dye curves were obtained from blood withdrawn through a subclavian artery and a cuvette densitometer<sup>11</sup> at 38.2 ml/min. The dye curves were recorded on a linear recorder (5) and blood was immediately reinjected into the dog. Curves were obtained after successive injections of known quantities of cardio-green dye into the main pulmonary artery, into the lobar pulmonary artery, and into the left atrium. The value for flow through the normally perfused lobes was taken as the difference between the average values for cardiac output obtained from two sets of these three curves and from the value for flow through the pump-perfused lobe. The value for blood volume of each region of the lung was obtained by multiplying the

mean transit time across the region by the rate of blood flow in the region. The difference in mean transit times, determined from the arterial dye-dilution curves from the main pulmonary artery injections and from the left atrial injection, was taken as the mean transit time across that part of the lung; the difference between the transit times of the arterial dye-dilution curve from the lobar arterial injection and the left atrial injection was taken as the mean transit time across the pump-perfused lobe. A detailed description of this technique has been reported (16, 17).

*Lobar perfusion with blood acidified with hydrochloric, lactic and acetic acids, and with hypercapnia.* In an initial group of 46 dogs, vasopressor responses to lowering the pH of the blood perfusing the separated lobar artery by introducing various acidifying agents were compared. After obtaining control pressures, blood samples, and dye curves in 16 dogs, 0.3 M HCl<sup>12</sup> was infused at 3.82 ml/min into the blood at the point of its withdrawal through the catheter in the femoral region, and 0.3 M sodium bicarbonate was infused into the left atrium at the same rate. In eight dogs, right atrial blood was used for perfusion and in another eight, aortic blood was used. Infusions were generally maintained for 4–4.5 min until the pH of blood perfusing the lobar artery decreased to approximately 7.1–7.0 units. Vascular and intrathoracic pressures were monitored continuously during the infusions, and usually for an additional 15–20 min, until pressures returned to near control levels. Additional blood samples were removed during the 4th min for pH, and gas analyses, and for dye-dilution curves. In

<sup>10</sup> Model 113-52, Instrument Laboratories, Boston, Mass.

<sup>11</sup> Gilford Instrument Laboratories, Oberlin, Ohio.

<sup>12</sup> All infused acids were Fisher Certified Reagents.

TABLE I  
Changes in Mean Pressures and Flow during Perfusion of Isolated Lobe with Acids (Mean Values  $\pm$ SE)

	Vascular pressures										Blood flow						
	LPA		MPA		LPVS		LA		RA		FA		SPL		NPL		
	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	
	<i>mm Hg</i>										<i>ml/kg per min</i>						
HCl infusions																	
Arterial (8 dogs)	13.5 $\pm 0.4$	36.9* $\pm 1.8$	22 $\pm 0.9$	23 $\pm 1.3$	7.6 $\pm 0.4$	12.0* $\pm 1.3$	3.1 $\pm 0.1$	3.1 $\pm 0.1$	1.9 $\pm 0.1$	1.8 $\pm 0.1$	127 $\pm 4.8$	127 $\pm 5.7$	17.5 $\pm 0.7$	17.5 $\pm 0.7$	194 $\pm 13.2$	193 $\pm 9.0$	
Venous (8 dogs)	14.7 $\pm 0.8$	37.5* $\pm 2.5$	23 $\pm 0.8$	24 $\pm 1.1$	7.5 $\pm 0.4$	11.2* $\pm 0.8$	3.0 $\pm 0.1$	3.1 $\pm 0.1$	1.8 $\pm 0.1$	1.8 $\pm 0.1$	131 $\pm 5.3$	132 $\pm 6.7$	18.3 $\pm 2.3$	18.3 $\pm 2.3$	181 $\pm 16.6$	170 $\pm 14.3$	
Lactic acid infusions																	
Arterial (7 dogs)	15.1 $\pm 0.7$	21.1* $\pm 2.1$	24.9 $\pm 1.9$	24.6 $\pm 1.8$	8.7 $\pm 0.5$	10 $\pm 0.8$	3.5 $\pm 0.5$	3.5 $\pm 0.5$	2.3 $\pm 0.5$	2.3 $\pm 0.5$	118 $\pm 8$	119 $\pm 8$	14.4 $\pm 4$	14.4 $\pm 4$	—	—	
Venous (3 dogs)	10 14 19	16 18 24	20 28 31	20 29 31	6 8 8	7 8 8	3.0 4.0 3.0	3.5 4.0 3.5	2.0 4.0 2.0	2.0 4.0 2.0	115 135 130	120 135 130	12 18 13	12 18 13	—	—	
Acetic acid infusions																	
Arterial (7 dogs)	16.0 $\pm 1.1$	21.1* $\pm 1.5$	21 $\pm 1.0$	22 $\pm 0.8$	8.0 $\pm 0.6$	8.8 $\pm 0.8$	2.7 $\pm 0.3$	2.7 $\pm 0.3$	1.5 $\pm 0.2$	1.5 $\pm 0.2$	124 $\pm 3$	124 $\pm 3$	16.2 $\pm 4$	16.2 $\pm 4$	—	—	
Venous (3 dogs)	17 14 18	23 19 22	25 18 18	24 19 18	7 6 8	8 7 8	3 3 4	3 3 4	1.5 2.0 2.0	1.5 2.0 2.0	130 118 115	130 118 115	18 19 12	18 19 12	—	—	
Carbon dioxide																	
Arterial (4 dogs)	14 14 14 18	12 15 16 18	21 19 22 25	18 19 20 25	7 7 6 7	6 7 6 7	2 4 3 2	2 4 3 2	2.0 2.0 1.0 2.0	2.0 2.0 1.0 2.0	90 130 135 125	95 130 140 130	10.2 19.1 10.0 8.1	10.2 19.1 10.0 8.1	179 202 200 164	188 194 206 172	
Venous (6 dogs)	15 $\pm 0.8$	15 $\pm 0.9$	22.8 $\pm 1.7$	21.0 $\pm 1.4$	7.3 $\pm 0.7$	7.1 $\pm 0.8$	2.8 $\pm 0.7$	3.0 $\pm 0.9$	1.5 $\pm 0.2$	1.5 $\pm 0.2$	125 $\pm 10$	120 $\pm 8$	12.2 $\pm 0.7$	12.2 $\pm 0.7$	196 $\pm 10.8$	189 $\pm 14$	

LPA, lobar perfused artery; MPA, main pulmonary artery; LPVS, small pulmonary vein in the perfused lobe; LA, left atrium; RA, right atrium; FA, femoral artery; SPL, separately perfused lobe; NPL, normally perfused lobes; C, control measurements; A, measurements during 4th min of acidemia; arterial (aortic) or venous (right atrial) refer to type of blood used for lobar arterial perfusions (mean values  $\pm$ SE).

\*  $P = 0.05$  or less.

three additional experiments, additional blood samples were removed from the isolated lobar artery for blood viscosity studies by the method of Wells, Denton, and Merrill (19) and for electrophoresis by the method of Korotzer, Banquist, and Searcy (20); and of Kohn (21) using Sephadex III strips in a Gleman Deluxe Rapid Electrophoresis Chamber. After the lobar arterial pressure had been increased 30–35 mm Hg during rapid extracorporeal infusions of 0.3 M HCl in three other dogs, lung biopsies were obtained within 15–30 sec after rapid thoracotomy was accomplished, and the specimens quickly fixed for light and electron microscopy. These sections were always obtained during perfusion with the acidemic blood from the mid-portion of the pump-perfused lobe and from a comparable site in the normally perfused lobe. Additionally, Wright stains were prepared with blood removed from the lobar arterial catheter during HCl infusion and also from the cut surface of the normally perfused and pump-perfused lobes at thoracotomy. In four other studies, blood from a pump-perfused lobar vein was removed before and during HCl infusions for platelet counts and plasma hemoglobin levels.

In ten other dogs, the pH of blood perfusing the separated lobar artery was similarly lowered to 7.1–7.0 units by infusions of 0.3 M lactic acid at rates of 5.1–7.0 ml/min for 4–4.5 min. In an additional 10 dogs, the pH was lowered by infusions of 0.3 M acetic acid at rates of 4.0–6.7 ml/min.

Right atrial blood was used for perfusion in three of the lactic acid infusions, and in three of the acetic acid infusion; aortic blood was used in the others. During all acid infusion, 0.3 M sodium bicarbonate was simultaneously infused into the left atrium at equal rates. In 10 other dogs, the pH of the lobar arterial blood was decreased by increasing the  $P_{CO_2}$  of the perfused blood. In six, right atrial blood was perfused, and in the other four, aortic blood was used. In these experiments, a Peirce-Emory membrane oxygenation (22, 23) was incorporated in the extracorporeal system between the Sarns pump and the lobar arterial perfusion catheter. During a control period of 15–20 min, air with 3%  $CO_2$  was delivered at 5.0 liters/min through the oxygenator. The gas mixture was then changed to 35–50%  $CO_2$  in air delivered at 5 liters/min. Care was used to maintain shim pressure at 185 mm Hg, so that perfusion pressure was not mechanically altered by the membrane oxygenator. Pressures were monitored continuously, and dye-dilution curves were obtained after 15–20 min of perfusion of the separated lobar artery with hypercapnic blood. At the end of four of the hypercapnic blood perfusions, the lobar vessels were tested for reactivity to infusions of serotonin, 6.0  $\mu$ g/kg per min for 4 min, and an abrupt pressor response, similar to that previously reported with this technique (24) was found in each experiment; after air with 3%  $CO_2$  was resumed in three other experiments, infusions of lactic or acetic acid

TABLE II  
Changes in Blood Gases and pH Produced by

	Blood pH						Blood Po <sub>2</sub>	
	LPA		LPV		SA		LPA	
	C	A	C	A	C	A	C	A
	<i>pH units</i>						<i>mm Hg</i>	
HCl infusions								
Arterial	7.31	7.11*	7.35	7.18*	7.31	7.30	117	124
(8 dogs)	±0.02	±0.02	±0.01	±0.02	±0.02	±0.01	±9.7	±10.4
Venous	7.30	7.12*	7.35	7.17*	7.36	7.34	43	46
(8 dogs)	±0.02	±0.02	±0.01	±0.02	±0.02	±0.01	±1.2	±1.0
Lactic acid infusions								
Arterial	7.38	7.00*	7.42	7.15*	7.38	7.34	138	157
(7 dogs)	±0.02	±0.03	±0.02	±0.03	±0.03	±0.03	±15	±14
Venous	7.39	7.13	7.42	7.16	7.44	7.42	47	69
(3 dogs)	7.30	7.05	7.34	7.18	7.32	7.35	40	45
	7.38	7.00	7.41	7.17	7.34	7.34	44	41
Acetic acid infusions								
Arterial	7.38	7.16*	7.41	7.23*	7.38	7.37	156	174
(7 dogs)	±0.03	±0.02	±0.01	±0.02	±0.02	±0.02	±11	±16
Venous	7.31	7.12	7.34	7.18	7.34	7.36	46	51
(3 dogs)	7.40	7.18	7.42	7.24	7.38	7.38	60	81
	7.38	7.15	7.40	7.22	7.40	7.38	42	48
Carbon dioxide								
Arterial	7.32	7.01	7.40	7.34	7.38	7.38	109	115
(4 dogs)	7.35	7.20	7.37	7.24	7.37	7.37	92	84
	7.40	7.10	7.46	7.26	7.39	7.35	102	106
	7.38	7.08	7.48	7.29	7.38	7.38	97	88
Venous	7.37	7.03*	7.44	7.32*	7.36	7.34	51	56
(6 dogs)	±0.01	±0.04	±0.03	±0.03	±0.01	±0.01	±2.9	±3.6

See footnotes Table I; LPV, pulmonary venous blood from pump-perfused lobe; SA, systemic arterial blood (mean values SE).

\*  $P = 0.05$  or less.

similarly lowered lobar arterial blood pH, but increased lobar arterial pressure 4–7 mm Hg.

*Lobar perfusion with blood acidified and then returned to control pH during extracorporeal circulation (EHNaT blood).* In 10 dogs, 0.3 M HCl was infused at 1.91 ml/min for 4 min into the aortic blood as it was being withdrawn from the femoral region, and 0.3 M sodium bicarbonate and 0.3 M Tris were also infused separately at that same rate into the blood downstream to the pump, near the balloon catheter (blood so treated extracorporeally is abbreviated EHNaT). Changes in pH of the blood actually perfusing the separated lobar artery were therefore avoided. (In six initial studies, infusions of 0.3 M HCl alone at 1.91 ml/min caused the pH of the perfusing blood to decrease 0.06–0.17 units; the resulting pressor response in the separated lobar artery, however, was of the same magnitude as that found when the pH had been returned to its original level. Other studies in four dogs indicated that the pressure in the pump-perfused lobar vessels were not changed

by the infusions of 0.3 M Tris alone, and these pressures decreased 1.8–3.6 mm Hg during infusions of 0.3 M sodium bicarbonate.) Studies similar to those obtained in the previous group were obtained, but dye-dilution curves were omitted. In four other dogs, the perfused aortic blood was initially acidified with 0.3 M acetic acid infused at 4.0–6.7 ml/min, and 0.3 M sodium bicarbonate and 0.3 M Tris were infused at 1.9–2.6 ml/min downstream. In three of these studies during acidification with HCl and pH correction, and in two with acetic acid, blood was removed from the perfused lobar artery during the control period and at the 4th min and was examined for potassium concentration.

*Lobar perfusion with acidified blood which had previously perfused other regions.* In 7 dogs, EHNaT aortic blood was pump-perfused into a cannulated femoral artery, which had been ligated proximal to the site of perfusion. Blood from the ipsilateral femoral vein was withdrawn through a second Sarns pump and delivered to the hemodynamically separated lobar artery of the dog. The flow rates through

*Acidifying Lobar Arterial Blood (Mean Values  $\pm$ SE)*

Blood Po <sub>2</sub>		Blood Pco <sub>2</sub>					
SA		LPA		LPV		SA	
C	A	C	A	C	A	C	A
<i>mm Hg</i>		<i>mm Hg</i>					
117	112	38	49*	33	41*	39	43
$\pm 9.5$	$\pm 6.7$	$\pm 2.4$	$\pm 2.1$	$\pm 1.9$	$\pm 2.5$	$\pm 2.0$	$\pm 1.7$
130	129	45	55*	39	48*	41	39
$\pm 6.8$	$\pm 6.6$	$\pm 2.7$	$\pm 3.8$	$\pm 2.2$	$\pm 3.4$	$\pm 2.3$	$\pm 2.2$
148	168	45	72*	30	40*	42	40
$\pm 13$	$\pm 8$	$\pm 3$	$\pm 3$	$\pm 2$	$\pm 2$	$\pm 2$	$\pm 2$
218	216	35	58	31	42	32	34
92	90	55	71	41	61	43	38
220	210	34	44	31	34	34	40
160	145	40	54*	34	44*	40	41
$\pm 10$	$\pm 12$	$\pm 2.1$	$\pm 2.4$	$\pm 2.0$	$\pm 1.9$	$\pm 2.6$	$\pm 2.2$
92	91	38	54	34	48	42	40
138	138	41	59	38	51	38	39
90	90	46	66	40	52	42	46
116	110	37	98	27	55	35	37
94	98	35	89	30	47	38	41
115	120	24	98	22	50	32	33
92	110	35	91	24	42	31	36
127	114	41	99*	31	47*	35	37
$\pm 9.2$	$\pm 6.9$	$\pm 2.0$	$\pm 5.7$	$\pm 2.6$	$\pm 2.4$	$\pm 2.1$	$\pm 2.4$

both pumps were equal, and adjusted so that the mean femoral arterial pressure 2-3 cm downstream to the perfusion site was as near mean aortic pressure as the pumping system permitted. Infusions were delivered at the rate of 1.91 ml/min, and were continued for 6-10 min. Blood samples from the pump-perfused femoral artery and the pump-perfused lobar artery were analyzed for pH, Pco<sub>2</sub>, and Po<sub>2</sub>.

Eight other dogs were similarly prepared except that an 18F polyethylene catheter was introduced from an external jugular vein, and passed transeptally through the left atrium into a large right pulmonary vein. Blood removed through this right pulmonary venous catheter was then pump-perfused at a constant rate of flow through the special balloon perfusion catheter into the hemodynamically separated artery in the left lower lobe. Additional catheters were inserted for continuous monitoring of pressure, sampling of blood, and measuring pulmonary blood flow by methods described above. After pump perfusing for 15-20 min to ensure stabilization, 0.3 M HCl was infused into the right pulmonary

artery at 3.82 ml/min for 15-20 min, until the pH of blood in the main pulmonary artery had decreased to approximately 7.10-7.00 units. Since balloon distention in the left lobar artery diverted most of the right ventricular blood into the right pulmonary artery, infusions of HCl produced systemic acidemia in all these dogs. Blood flow, blood pH, Pco<sub>2</sub> and Po<sub>2</sub> were studied during the control period, after 8-10 min of infusion, and at the end of the experiment. After each of these experiments, the acidified pulmonary venous blood, which perfused the separated lobar artery, was extracorporeally infused with 0.3 M HCl, sodium bicarbonate, and Tris at 1.91 ml/min for 2-3 min. Studies similar to the earlier experiments were then obtained.

*Femoral arterial perfusion with EHNaT blood which had perfused the lobar vessels.* During six other lobar arterial perfusions with EHNaT aortic blood, blood from the pump-perfused lobar vein was withdrawn with a transeptally placed lobar venous catheter, and simultaneously perfused with a second pump into a cannulated femoral artery by

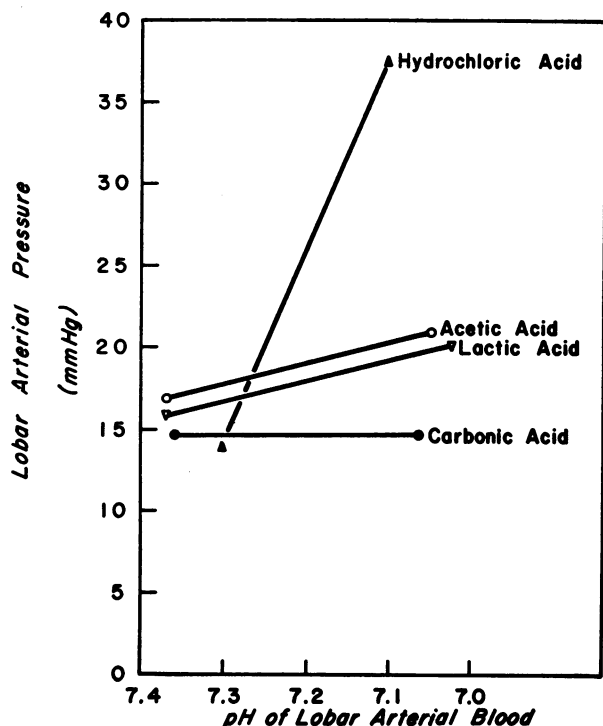


FIGURE 2 Relationship of changes in mean lobar arterial pressure to decreases in pH of blood perfusing the lobe. Decreases in blood pH to nearly the same level with different acidifying agents caused different responses.

methods described above. Pressures were monitored continuously in the perfused arteries and blood samples were obtained from these sites for pH,  $P_{O_2}$ , and  $P_{CO_2}$  during

the control period and during 5 min of lobar arterial perfusion with EHNaT blood.

*Lobar arterial perfusion with acidified dextran.* In five other experiments, 4% low molecular weight dextran<sup>18</sup> in normal saline with pH adjusted to 7.35–7.40 with bicarbonate and was perfused at 37°C into the hemodynamically separated lobar artery at gradually increasing rates until the pressures in that vessel approximated the pressure in the main pulmonary artery before balloon distention. The perfused dextran, admixed with small amounts of blood from neighboring areas, was simultaneously removed from the perfused lobar vein through a transeptally placed 18F polyethylene catheter, using the same Sarns pump-head to insure equal perfusion and withdrawal rates. Preliminary studies with this technique in four open-chest dogs indicated that after 1–2 min of dextran perfusion, the lobe became white, and fluid removed from small veins near the parenchyma was clear. The hematocrit value of the withdrawn dextran was usually below 6%, and the greatest fall in systemic arterial hematocrit during these experiments was 5% (from 41 to 36%). Histologic sections of the lobe, however, did reveal a sparse number of red cells, when compared with sections from the contralateral lobes. After the separated lobar artery had been perfused with dextran for 6–8 min, and all pressures stabilized, 0.3 M HCl was infused into the dextran as it entered the perfusion catheter. The rate of acid infusion was increased at 3 min intervals until a pressor response was observed. The pH of the lobar arterial perfusate was determined before each increment in infusion rate. The initial infusion rate was 0.05 ml/min, and the last infusion rate was usually 0.91–1.09 ml/min. The pressor response was then observed for 1–2 min before the acid infusion was stopped, and the lobar arterial pressure was monitored until it returned to or near control levels. After lobar arterial pressure had returned to control levels in three studies, serotonin was infused into the dextran perfusate

<sup>18</sup> Generously supplied by Pharmacia Laboratories, Atlanta, Ga. and by Abbott Laboratories, Chicago, Ill.

TABLE III  
Effects of Infusions of 0.3 M HCl (1.91 ml/min)

	Vascular Pressures								
	Min. . . . .	LPA				LPVS			
		C	4	6	8	C	4	6	8
					<i>mm Hg</i>				
0.3 M HCl (6 dogs)	17.2 ±0.9	26.2* ±1.4	29.0* ±0.9	30.8* ±1.6	8.3 ±0.67	8.7 ±0.61	11.1 ±1.0	11.7* ±0.75	
EHNaT   (HCl) (10 dogs)	16.8 ±0.8	24.4* ±1.9	26.4* ±1.7	27.1* ±1.5	6.1 ±0.3	7.4 ±0.8	8.2* ±0.7	8.5* ±0.8	
EHNaT   (Acetic acid) (4 dogs)	17 16 15 16	21 22 29 20	19 19 18 18	17 16 15 15	6 5 7 6	7 6 7 8	6 5 7 6	6 5 7 6	

See footnotes Table I.

\*  $P = 0.05$  or less.

‡ Refers to blood extracorporeally infused with acid, bicarbonate, and Tris.

|| Infusions maintained 4 min, and measurements obtained at end of infusion and 2 and 4 min later.



in doses similar to those used in the studies with hypercapnia, and a similar abrupt pressor response was noted (24). In two similar dextran perfusion studies, no pressor response was observed during similar infusions of saline instead of 0.3 M HCl for comparable periods of time. No gross edema was evident on inspection of the lobes by thoracotomy at the end of each study.

*Lobar arterial perfusion with acidified blood during apneic periods.* In three similarly prepared dogs, transient periods of apnea were produced by first ventilating the animals with 100% oxygen by positive pressure breathing for 20–25 min, and then abruptly disconnecting them from the respirator. Since airflow was absent during the ensuing 3–4 min of apnea, the effect of bronchoconstriction on the vascular responses was greatly diminished (19). The lobe was perfused with aortic blood and intralobar infusions of 0.3 M HCl (3.82 ml/min) were commenced just after the apneic period began. In two control studies, in which equal volumes of normal saline were infused into the blood perfusing the lobe during the apneic period, no changes in vascular pressures were observed.

## RESULTS

*Lobar perfusion with bloods acidified with the different acids.* Infusions of 0.3 M HCl at 3.82 ml/min into blood which was pump perfused into a separated lobar artery, increased the pressure in that vessel greatly, and increased pressure in the lobar small vein slightly but significantly ( $P < 0.01$ ) (Tables I and II, Fig. 2). These vasopressor responses were similar during perfusion of the lobar artery with right atrial and systemic arterial blood and while spontaneously breathing air or 35% oxygen. The  $P_{O_2}$  of the systemic arterial blood was either normal or increased during perfusion with acidic blood and was similar to that of the blood in the vein from the

pump-perfused lobe. These responses usually began 1–2 min after beginning the infusion; the peak response was reached in 3–4 min after beginning the infusion and persisted for 8–10 min. Lobar vascular pressures generally returned to control levels in 15–20 min. Pressures in the systemic and main pulmonary arteries, the right and left atria, and the pleural space were unchanged, and the values for blood flows in the normally perfused and pump-perfused lobes were not significantly altered ( $P > 0.20$ ). The mean value for pH of lobar arterial blood decreased from 7.30 to 7.12 units and the value for pH of the lobar venous blood decreased from 7.35 to 7.18 units; the mean value for  $P_{CO_2}$  rose significantly ( $P < 0.05$ ), but the mean value for  $P_{O_2}$  was unchanged. The values for systemic arterial and main pulmonary arterial blood pH,  $P_{CO_2}$  and  $P_{O_2}$  were not significantly altered. Infusions of 0.3 M lactic acid moderately but significantly ( $P < 0.01$ ) increased the pressure in the pump-perfused lobar artery, but did not significantly change pressure in the lobar small vein (Tables I and II, Fig. 2). The other vascular pressures and the pleural pressure remained unchanged during lactic acid infusions. The mean value for lobar arterial blood pH decreased from 7.38 to 7.00 units; the value for  $P_{CO_2}$  increased significantly ( $P < 0.05$ ), and the mean value for  $P_{O_2}$  was not significantly changed. The values for pH,  $P_{CO_2}$  and  $P_{O_2}$  of systemic and main pulmonary arterial blood were unchanged. Infusions of 0.3 M acetic acid moderately but significantly ( $P < 0.01$ ) increased the pressure in the perfused lobar artery, and did not significantly increase pressure in the lobar small vein (Tables I and II, Fig. 2). The pressor response to acetic acid infusions was not significantly

### and of Perfusion with EHNaT $\ddagger$ Blood

Vascular Pressures				Lobar Blood					
LA				pH		$P_{O_2}$		$P_{CO_2}$	
C	4	6	8	C	4	C	4	C	4
mm Hg				mm Hg		mm Hg		mm Hg	
2.8	2.7	2.7	2.8	7.34	7.25*	129	139	42	49*
$\pm 0.2$	$\pm 0.3$	$\pm 0.2$	$\pm 0.7$	$\pm 0.02$	$\pm 0.03$	$\pm 3.4$	$\pm 3.5$	$\pm 2.0$	$\pm 2.3$
2.3	2.3	2.4	2.4	7.37	7.39	156	158	43	51
$\pm 0.3$	$\pm 0.2$	$\pm 1.7$	$\pm 0.2$	$\pm 0.02$	$\pm 0.02$	$\pm 12$	$\pm 14$	$\pm 2.8$	$\pm 3.4$
3	3	3	3	7.36	7.37	128	132	42	44
2	2	2	2	7.34	7.36	140	145	48	50
4	4	4	4	7.35	7.33	140	148	40	53
3	3	3	3	7.39	7.37	129	132	37	50

TABLE IV  
Lobar Response to Perfusion with Femoral and Pulmonary Venous Blood

	Femoral venous EHNaT blood perfusion (6 dogs)		Pulmonary venous blood perfusion (8 dogs)		
	C	5 min	C	5 min	18 min
Mean vascular pressure, <i>mm Hg</i>					
LPA	15.1 ± 0.8	22.8* ± 1.3	15.0 ± 0.8	14.7 ± 0.9	15.5 ± 0.8
LA	3.0 ± 0.45	3.0 ± 0.45	2.3 ± 0.6	2.3 ± 0.5	2.8 ± 0.6
RA	1.5 ± 0.30	1.5 ± 0.30	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
MPA	20 ± 1.0	20.5 ± 1.2	21.3 ± 1.5	24.0 ± 2.2	27.4* ± 2.4
Aorta	104 ± 10.9	101 ± 10.4	107 ± 10	105 ± 10	105 ± 10
PFA	89 ± 4.9	59* ± 4.6			
Lobar arterial blood					
pH	7.31 ± 0.3	7.30 ± 0.3	7.34 ± 0.1	7.33 ± 0.1	7.12 ± 0.03
Po <sub>2</sub> , <i>mm Hg</i>	48 ± 4.5	53 ± 4.6	135 ± 13		137 ± 14
Pco <sub>2</sub> , <i>mm Hg</i>	45 ± 2.4	51 ± 3.0	40 ± 2.4		48* ± 2.3
PFA					
pH	7.36 ± 0.03	7.34 ± 0.03			
Aortic blood					
pH			7.36 ± 0.01	7.33 ± 0.01	7.16* ± 0.03
Blood flow, <i>ml/kg per min</i>					
NPL			197 ± 8.1	181 ± 8.8	175 ± 8.9
SPL	11.4 ± 4.8	11.4 ± 4.8	10.1 ± 4.1	10.2 ± 4.1	10.2 ± 4.1

See footnotes Table I. PFA, pump-perfused femoral artery.

\*  $P = 0.05$  or less.

different from the response to lactic acid infusions. The pressor responses to both acids usually persisted for 3–5 min after cessation of the infusions. The values for the other vascular pressures, pleural pressure, and blood flow through the normally perfused lobes were unchanged. During acetic acid infusion, the mean value for lobar arterial blood pH decreased from 7.38 to 7.16 units; the mean value for Po<sub>2</sub> was unchanged. Pump perfusion of the lobar artery with aortic or right atrial blood rendered hypercapnic with the membrane oxygenator caused no significant changes in vascular or pleural pressures (Tables I and II, Fig. 2). Changes in blood flow in the normally perfused lobes were not significant. The mean value for lobar arterial blood pH decreased from 7.36 to 7.06 units; the value for Pco<sub>2</sub> increased greatly and the mean value for Po<sub>2</sub> was unchanged. The values for pH, Pco<sub>2</sub>, and Po<sub>2</sub> in systemic and main pulmonary arterial blood were unchanged. In each of these groups of experiments with acidemic bloods, no systematic differences in lobar arterial pressure responses were found during perfusions with systemic arterial and right atrial blood, or while spontaneously breathing ambient air or 35% oxygen (Table I); during these experiments, the blood in the separated lobar vein and systemic arteries was at normal or increased Po<sub>2</sub> values.

*Lobar perfusion with EHNaT blood.* Infusions of 0.3 M HCl at 1.91 ml/min for 4 min into the aortic blood which perfused the separated lobar artery also increased the lobar vascular pressures and decreased the pH of perfused blood, but these responses were not as great as those produced by infusions at 3.82 ml/min (Table III). However, lobar vasopressor responses also occurred during simultaneous infusions of 0.3 M HCl (1.91 ml/min for 4 min) into the aortic blood as it was removed from the femoral region and 0.3 M sodium bicarbonate and 0.3 M Tris into the blood as it entered the perfusion catheter. The magnitude and duration of these pressor responses were similar to those in which 0.3 M HCl alone was infused at 1.91 ml/min; the pressure in the lobar artery increased moderately but significantly ( $P < 0.01$ ) and this pressor response was usually maintained for 10–15 min after cessation of the infusions (Table III). Pressure in the lobar small vein increased slightly, but significantly ( $P < 0.05$ ); the pressures in the systemic and main pulmonary arteries, the right and left atria and pleural space were not significantly changed. The value for the mean pH of lobar arterial blood was unchanged in these experiments and in no experiment did this value fall more than 0.03 units. The plasma potassium values for lobar arterial blood in

three experiments were 4.1, 4.0, and 3.7 mEq/liter before infusions of HCl, bicarbonate, and Tris, and were 4.3, 3.9, and 3.9 mEq/liter at the peak of the pressor response during the infusions. Similarly, simultaneous infusions of 0.3 M acetic acid, bicarbonate, and Tris also increased the lobar arterial pressure without changing the value for pH of blood actually perfusing the lobar artery (Table III). In two of these experiments, plasma potassium values for lobar arterial blood were 3.8 and 3.5 mEq/liter, and 3.7 and 3.8 mEq/liter at the peak of the pressor response.

*Lobar arterial perfusion with acidified blood which had perfused other regions.* Pump perfusion of a cannulated femoral artery with EHNaT aortic blood caused a significant ( $P < 0.05$ ) fall in pressure in that perfused artery; the pressure in the separated lobar artery, which was simultaneously perfused with blood from the ipsilateral femoral vein, increased significantly ( $P < 0.01$ ) (Table IV). Pressure in the subclavian and main pulmonary arteries and the right and left atria were not significantly changed. The values for pH and  $P_{O_2}$  of blood removed from the pump-perfused femoral and lobar arteries were not significantly changed by the infusions. However, pump perfusion of the cannulated femoral artery with EHNaT blood which had previously perfused the separated lobar vessels did not change the pressure in the perfused femoral artery in six other studies (Table V).

In eight other experiments, 0.3 M HCl was infused through a small teflon catheter into the right pulmonary artery for 10–15 min, while blood removed from a right pulmonary vein was simultaneously pump perfused into the separated lobar artery. Infusions of HCl increased the main pulmonary arterial pressure significantly ( $P < 0.05$ ), but pump perfusion with the acidified pulmonary venous blood did not significantly change the pressure in the separated lobar artery. Pressures in the systemic artery, and the left and right atria were also unchanged (Table IV). The blood flow through the normally perfused lung vessels was not significantly changed. The mean value for pH of systemic arterial blood decreased

from 7.36 to 7.16 and the mean value for pH of blood perfusing the separated lobar artery decreased from 7.34 to 7.12 units. At the end of these experiments extracorporeal infusions of 0.3 M solutions of HCl, sodium bicarbonate and Tris into the acidified pulmonary venous blood at rates of 1.91 ml/min always caused an abrupt increase in perfused lobar arterial pressure. This pressor response ranged from 8 to 14 mm Hg, without additional change in pH of the acidified pulmonary venous blood.

*Lobar perfusion with acidified dextran.* During perfusion of the separated lobar artery with acidified dextran, no pressor response occurred in that vessel until the value for the pH of the perfusate had decreased below a level ranging from 6.40 to 5.80 units (Table VI). Since, in each experiment, the pH of the perfusate decreased abruptly at the last change in HCl infusion rate, the exact pH level at which the pressor response commenced could not be determined. The pressor response in each experiment began 20–30 sec after the highest rate of infusion had been reached, and the pressure usually increased 15–20 mm Hg in the succeeding 30 seconds. The pressures returned to near control levels 8–12 min after the HCl was stopped. Pressures in the systemic and main pulmonary arteries, and in the right and left atria were unchanged during the dextran perfusions.

Conglutination of formed elements were not seen on examination of Wright stains of perfusing blood or blood obtained from cut lung sections. The values for lobar venous platelet count in four studies were not changed during HCl infusions (average control, 110,000/mm<sup>3</sup>; average with acid, 115,000 mm<sup>3</sup>; greatest fall with acid was 10% of control value). The changes in plasma hemoglobin during HCl infusions were small and inconstant in four studies (average control 25 mg per 100 ml; average with acid, 30 mg per 100 ml; and in two of the four, this value was unchanged). No changes in blood viscosity or electrophoretic pattern were found. Conglutination of formed elements was not found on examination of the pump-perfused and control lobes by light microscopy. Additionally, examination by electron mi-

TABLE V  
Femoral Arterial Pressure Changes during Perfusion with Lobar Venous EHNaT Blood in 6 Dogs (Mean Values  $\pm$ SE)

Mean vascular pressures										Blood				PFA blood gases			
PFA		LPA		LA		Aorta		MPA		LPA		PFA		$P_{O_2}$		$P_{CO_2}$	
C	5	C	5	mm Hg		C	5	C	5	pH		C	5	mm Hg		C	5
	min		min	C	5	C	5	C	5	C	5	C	5	C	5	C	5
89	89	16.2	25.8*	2.0	2.0	108	104	21	21	7.36	7.35	7.40	7.39	128	130	42	46
$\pm 6.0$	$\pm 5.7$	$\pm 1.1$	$\pm 1.4$	$\pm 0.1$	$\pm 0.1$	$\pm 7.2$	$\pm 7.2$	$\pm 0.7$	$\pm 0.8$	$\pm 0.01$	$\pm 0.01$	$\pm 0.02$	$\pm 0.02$	$\pm 14$	$\pm 12$	$\pm 2$	$\pm 4$

See footnotes Table I. PFA, pump-perfused femoral artery.  
\*  $P = 0.05$  or less.

TABLE VI  
Changes in Mean Lobar Arterial Pressure with Acidified Dextran Infusions

	HCl infusion						Vascular pressures				Aortic blood					
	Control		No pressor* response		Pressor‡ response		Aorta		MPA		C		A		Hemoglobin	
	P-LPA§		P-LPA		P-LPA		C¶		C		C		A		mg/100 ml	
		pH		pH		pH		A**		A		pH		A		A
Dog 1	10	7.42	10	5.80	28	4.80	144	138	15	14	7.38	7.36	14.8	12.1		
2	12	7.40	12	6.00	32	4.60	120	120	18	16	7.34	7.34	15.0	11.4		
3	14	7.40	14	5.90	37	5.80	132	120	18	18	7.40	7.41	15.4	12.1		
4	16	7.48	16	6.22	34	5.28	128	120	22	22	7.33	7.34	14.1	11.0		
5	21	7.40	21	6.40	43	4.60	112	110	24	22	7.35	7.32	14.8	12.8		

\* Indicating the extent of fall in pH of perfused dextran (produced by progressively increasing the rate of HCl infusion into the dextran) without causing a perfused lobar arterial pressor response.

‡ Indicating the pH of perfused dextran at the point of lobar arterial pressor response to the last increment in rate of HCl infusion.

§ Mean pressure in dextran perfused lobar artery.

|| pH of dextran perfusing the lobar artery.

¶ Control values measured before commencing infusions of HCl into the dextran (all pressures are in mm Hg).

\*\* Values measured at time of lobar arterial pressor response to progressively increasing rates of HCl infusion.

crosscopy revealed no evidence of platelet aggregates or recently formed thrombi in blood vessels of the acid-perfused or control lobes of the three dogs examined.



FIGURE 3 Electron micrograph of acid-perfused lobe of lung: One group of erythrocytes (rouleau) is present in the capillary of an alveolar wall. No platelets are present and there is an absence of fibrin between the red blood cells composing the rouleau. The rouleau does not seem to have obstructed blood flow through this vessel.  $\times 10,000$ .

By contrast, rouleaux forms were frequently observed in the various blood vessels in both regions of the lung. No fibrin deposits or platelets were found between the red blood cells forming each rouleau. The rouleaux were frequently composed of approximately two to five red blood cells (Fig. 3). In one animal, however, rouleaux were especially abundant and large, being composed of up to 25 red blood cells. The rouleaux did not appear to have obstructed flow even in this particular animal.

One significant difference between control and pump-perfused lobes was the presence of large lucid phagolysosomes in neutrophils in blood vessels of the acid-perfused lobes. These vesicles measured up to  $1.9 \mu$  and contained only a small amount of granular material and, infrequently, small fragments of membranes. They were probably related to smaller organelles of the same type which were formed by invagination of the cell membrane. Disruption of the membranes of these vacuoles rarely occurred and was associated with other degenerative changes in the neutrophil including local breakdown of cytoplasmic matrix and dilation of the perinuclear space (Fig. 4). In the control lobes, neutrophils with large lysosomes were found much less frequently in a ratio of approximately 1:10. Occasionally, the neutrophils contained autolysosomes also, but no significant differences with regard to those organelles could be ascertained between perfused and control lobes. The lack of important differences was also noted in regard to basophils, mast cells, and endothelial cells which showed extensive pinocytosis. Platelets in both lobes were too few in number to merit comment.

## DISCUSSION

During pump perfusion of the hemodynamically separated lobar artery with aortic or right atrial blood, in-

fusions of 0.3 M HCl at a rate sufficient to lower pH of the lobar arterial blood to 7.10 units caused a marked increase in lobar arterial pressure and a small increase in pressure in the lobar small vein. Although similar decreases in pH of the blood perfusing the lobar artery followed infusions of 0.3 M acetic and lactic acids, the magnitude of the lobar arterial pressor response was significantly ( $P < 0.01$ ) less, and the pressure in the lobar small vein was unchanged. Similar decreases in pH of the perfusing blood produced by increasing the  $P_{CO_2}$  with a membrane oxygenator caused no pressor response. These data indicate that the magnitude of the lobar arterial pressor response to acidemia in this experimental preparation was not directly related to the pH of the blood actually perfusing the lobar artery, within the range 7.40–7.10. Since the pH of the lobar venous blood usually decreased 7.20–7.10 units during infusions of the three acids, these data additionally suggest that the response to infusions of acids was not directly related to the pH of the lobar venous blood. This interpretation of the present data is supported by the observation that perfusion of the separated lobar artery with right pulmonary venous blood having pH values which decreased to as low as 7.09 units did not cause a lobar arterial pressor response. Furthermore, the vasopressor response also occurred after extracorporeal adjustment of the pH of the acidified blood to control levels, so that the value for pH of blood actually perfusing the lobar artery was unchanged. Additionally, during perfusion with low molecular weight dextran, a vasopressor response was only observed when the pH of the perfusate was decreased below that range 6.35–5.65 with infusions of 0.3 M HCl. The very low pH values required to increase lobar arterial pressure during dextran perfusions might have been related to altered reactivity of these intact vessels during nonsanguineous perfusions. However, the magnitude of the vasopressor response to serotonin during dextran perfusions was similar to that previously observed with this preparation during perfusion of the lobar vessels with aortic or right atrial blood (24).

The magnitude of the differences in lobar arterial pressor responses to hydrochloric and acetic or lactic acids is greater in these experiments than in previous studies of acidemia in dogs (1, 10). Intravenous infusions of 0.3 M hydrochloric and lactic acids at 4 ml/min for 15–20 min into four intact dogs was reported to increase pulmonary arterial pressure moderately (average increase, 5 mm Hg with hydrochloric, and 3 mm Hg with lactic acid); in three, the changes in pulmonary blood flow were small (1). These differences may, in part, be related to divergent experimental designs. In the present studies, these acids were infused, extracorporeally, into blood which was directly pump per-

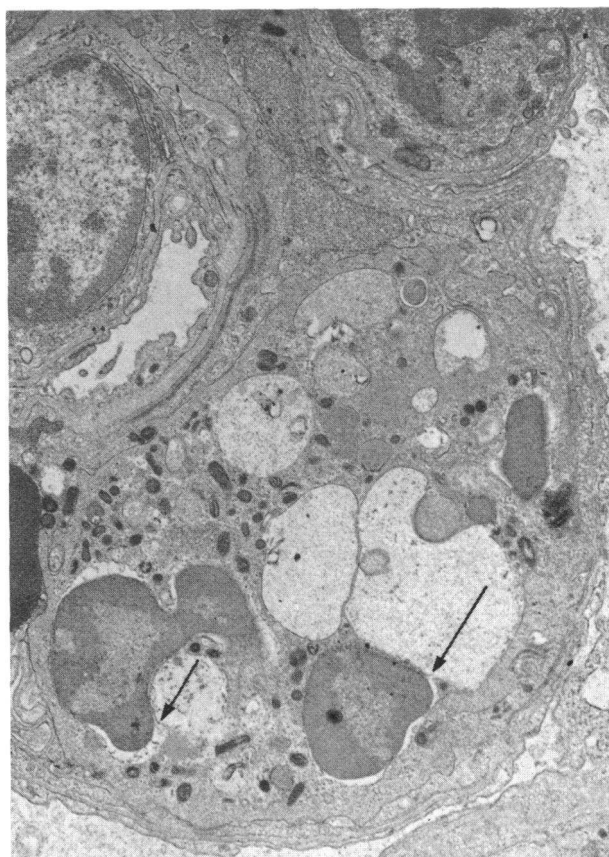


FIGURE 4 Electron micrograph of acid-perfused lobe of lung: A neutrophil is present within a capillary of the alveolar wall. It contains several lucid phagolysosomes, four of which are large. Two of them show disruption of their membranes (arrows), adjacent cytoplasmic breakdown, and continuity with dilated perinuclear spaces. Neutrophils with large lucid phagolysosomes were found more commonly in acid-perfused lobes.  $\times 48,000$ .

fused into a single lobe of one lung. During intravenous infusions into intact dogs (1), large differences in responses to any vasopressor substances that might have been activated by these acids could have been obscured by hemodilution or by other alterations of these substances. Additionally, the differences in pressor responses to similar amounts of these acids might have been more apparent in the present studies in which they were delivered to only a segment of one lung rather than more diffusely to both lungs (1). The large differences in pressor responses in the present experiments more closely resemble those reported by Lloyd (10). In his studies of lung lobes excised from dogs, infusions of acids, particularly hydrochloric, into the perfusion circuit caused large persistent pressor responses, unless the infusion rates were slow. Although the present hydrochloric acid infusion rate did not exceed Lloyd's

slower rate, the divergent pressor responses might also have been due to differences in experimental models. Since the pump-perfused lobe in the present study was not dissected or excised, and was perfused with blood which recirculated through the entire body of the animal, these lobar vessels might have been more sensitive to small differences in vasoactive substances than were the excised lobes in the previous study (10). Other studies (24) have shown that the pressor responses of the separated lobar vessels in this preparation to similar quantities of serotonin were greater than those reported with that excised lobe preparation (25). Additionally, the similar vasopressor responses during slow infusions of hydrochloric and lactic acids were largely observed in excised lobes which had superimposed severe ventilatory hypoxia; the vasopressor responses to slow acid infusions were attenuated or prevented by removal of the hypoxic stimulus (10). Lloyd's observations also lead him to suggest that the larger persistent pressor responses that he observed with rapid acid infusions might have been due to pressor substances liberated from the blood at the injection site. Large vasopressor responses, similar to those observed with hydrochloric acid, have previously been reported in dogs with infusions of serotonin (24), prostaglandin F<sub>2</sub> alpha (26), and injections of fibrinopeptides (27), and endotoxin (28).

The present studies afford no precise explanation for the differences reported (15) in other studies of the relationship of hypercapnic acidosis to pulmonary hypertension. A pulmonary arterial pressor response to ventilatory hypercapnia has generally been found (1-3, 6, 9, 13), and is usually attributed to vasoconstriction in intact animal and excised lobe experiments. However, a vasopressor response has been reported less frequently during perfusion of hypercapnic blood into lungs ventilated with air or higher oxygen mixtures (15). Moreover, Nisell found that perfusion of cat lungs with hypercapnic blood decreased pulmonary vascular resistance (13), and Viles and Shepherd have shown that the pulmonary vasopressor response to acidemia is greatly diminished by hypercapnia (6). Daly and Hebb (15) have also emphasized that the largest vasopressor responses to ventilatory hypercapnia are observed when the P<sub>CO<sub>2</sub></sub> of the blood perfusing the lung is maintained at low values. The present experiments, which demonstrate no vasopressor response to lobar perfusion with blood rendered acidic by severe hypercapnia are similar to those reported by Manfredi and Sieker (29) in open-chest dogs during lobar ventilation with air. These data, however, differ from other studies in which constant-flow perfusion of excised cat lungs with hypercapnic blood caused a vasopressor response, apparently from constriction of inflow (arterial) vessels (30), and to constant-pressure perfusion studies of excised dog lungs in which hyper-

capnic blood caused a transient decrease in outflow of blood and lobar hyperemia, apparently from constriction of outflow vessels (31). Divergent responses have also been shown to be related, in part, to the fact that cats are more responsive to hypercapnia than dogs (3). Other investigators have indicated that the pulmonary vessels of excised lung preparations are more responsive to hypercapnia than vessels of intact animals, and have attributed this difference to an influx of systemic hormonal agents (30), or to concomitant reflex changes (6) induced by hypercapnia in the intact animals. These factors are unlikely to have influenced the present results, since the P<sub>CO<sub>2</sub></sub> of systemic arterial blood and the blood flow and pressure in the systemic and main pulmonary arteries was unchanged during these experiments. Additionally, the absence of a pressor response to perfusion with hypercapnic blood might have been related to the fact that this acidemia was induced with a volatile acid, and the pH of the lobar venous blood did not reach the low levels found in lobar arterial blood. However, this explanation seems less attractive since perfusion of the separated lobe with right pulmonary venous blood, previously acidified to comparable or lower pH levels with hydrochloric acid, also failed to increase lobar arterial pressure.

In these experiments, the lobar vasopressor response to acidified blood was prevented by passage of this blood through the pulmonary vascular bed before it reached the separated lobar artery. Additionally, no pressor response occurred in the main pulmonary artery during infusions of acid into blood perfusing the separated lobar artery, and no depressor response was found in the cannulated femoral artery during perfusion at a constant flow with blood removed from the vein draining the EHNaT-perfused lobar artery. The present experiments further suggest that the lobar vasopressor response to acidemia is not prevented by passage of the acidified blood through the vascular bed of the hind limb, since perfusion of the separated lobar artery with femoral venous blood caused a vasopressor response during perfusion of EHNaT aortic blood into the cannulated ipsilateral artery. The possibility that the lobar vasopressor response to perfusion with EHNaT blood might have been attenuated by hemodilution or other alteration of vasoactive substance during passage through the hind limb cannot be completely excluded. Alternatively, attenuation might have resulted from escape into the inferior vena cava of quantities of vasoactive material too small to affect pulmonary arterial pressure, through vessels collateral to the cannulated femoral vein. Albeit, the modest difference in mean pressor response in these experiments and those during lobar arterial perfusion with similarly treated blood which had not passed through the hind limb was not significantly different ( $P > 0.05$ ).

Furthermore, the absence of a lobar arterial pressor response to perfusion with pulmonary venous blood rather than femoral venous blood is unlikely to be due entirely to hemodilution or inactivation of vasoactive substances. In each experiment, HCl infusions increased main pulmonary arterial pressure, and blood removed directly from a right pulmonary vein was perfused into the lobar artery, using the same extracorporeal perfusion circuit used for femoral vein perfusions. The difference in  $P_{O_2}$  of acidified pulmonary venous blood and the acidified but pH-corrected femoral venous blood used for lobar arterial perfusion is also unlikely to have caused the differences in pressor responses, since pressor responses were regularly observed during lobar arterial perfusions with acidified aortic blood with comparably high  $P_{O_2}$  values. Additionally, subsequent infusions of hydrochloric acid, bicarbonate, and Tris into this acidified pulmonary venous blood increased the pressure in the perfused lobar artery without changing the  $P_{O_2}$  or pH of the blood actually perfusing that vessel.

Although the cause of the lobar vasopressor response is not established by these experiments, active constriction of these vessels is suggested by the rise in pressure in these vessels perfused at a constant flow in the absence of change in left atrial or pleural pressure. Moreover, the exact site in the lobar circulation at which the constriction might have occurred is unknown, but these data suggest that vessels upstream to the lobar small veins, presumably the lobar arteries, were chiefly involved. The small pressor response in the lobar small veins suggests that a lesser constriction might also have occurred in those vessels during infusion of the strongest acid.

These experiments suggest that unidentified vasoactive substances, which were activated at or near the site of extracorporeal acid infusion and largely inactivated by passage through the lung might have caused active vasoconstriction in the lobar vessels. Studies of acidemia in excised dog lungs have previously directed attention to this possibility (10). Since the hydrogen ion concentrations of the perfused bloods near the infusion sites of the various acids were probably dissimilar, the differences in extent of the pressor responses might have been related to differences in vasoactive substances activated at these sites. Presumably, small amounts of the vasoactive material formed with hydrochloric acid were able to pass through the lung and increase pressure in the lobar vein. The mediation of the vasopressor responses might have been similar for hydrochloric and acetic acids since correction of the pH values of blood acidified with these acids did not prevent the vasopressor responses. Since plasma potassium levels of lobar arterial blood were unchanged, efflux of this ion is unlikely to have contributed to the vasoconstrictor response. Previ-

ous investigators have shown that pulmonary vasoconstrictor substances including fibrinopeptides, are present in serum, defibrinated blood, and blood treated with a variety of chemical agents including acids (32). Additionally, these substances have been suspected of being actively catabolized in the lung (27, 33, 34); pulmonary extraction or inactivation of serotonin and  $F_2$  alpha prostaglandin has been demonstrated (34, 35). The absence of a lobar vasopressor response to perfusion with severely hypercapnic blood is not clearly explained by these data, but might have been due to the failure of the pH of blood in the membrane oxygenator to reach levels low enough to activate sufficient amounts of vasoactive substances. Moreover, these data are not inconsistent with previous studies which indicated that hypercapnia may also exert a lobar vasodilating effect (6, 13, 15), which could have obscured any tendency for smaller amounts of vasoactive substances to raise lobar vascular pressures.

In the present experiments, however, the acidemia was produced under conditions which are not like the usual ones of developing metabolic acidosis or alveolar hypercapnia, in that strong acids were directly infused into blood which perfused only one lung lobe. The mediation of the present pressor responses and of those found in the more usual forms of experimental and clinical acidosis may therefore be dissimilar.

The present experiments are similar to previous studies which indicated that infusions of fixed acids increase pulmonary arterial pressure at normal or high levels of systemic arterial  $P_{O_2}$  (9). They additionally indicate that during ventilation with air or higher oxygen mixtures, the pressor response to acid infusions is not influenced by the  $P_{O_2}$  of blood perfusing the lobar vessels, within the ranges used in these experiments. Although the pressor response to acidemia is usually enhanced by hypoxia, the mediation of this effect is not clearly defined (1-9). The present studies afford no additional information, since these data were obtained in closed-chest dogs without systemic hypoxia.

Bronchoconstriction is unlikely to have contributed greatly to the pressor response in these experiments. Since extracorporeal infusions of the acids alone, or of hydrochloric or acetic acid with sodium bicarbonate and Tris caused a localized vasopressor response without evidence of systemic or main pulmonary arterial pressure changes, generalized bronchoconstriction is unlikely to have occurred. Although some airway obstruction might have occurred locally in the pump-perfused lobe from intralobar circulation of constrictor agents, this response is unlikely to have caused or modulated the vasopressor response since similar pressor responses were found with infusions of HCl during apneic periods. Additionally, during spontaneous breathing, the vasopressor response



was not accompanied by changes in respiratory rate, pleural pressure, or systemic arterial pH,  $P_{CO_2}$ , or  $P_{O_2}$ .

The possibility that conglutination of formed elements of blood might have caused or contributed to the vasopressor responses to infusions of these acidifying agents is not excluded by these studies. However, several observations suggest that the contribution of conglutination to the pressor response was probably not great. Obstruction of arterioles and venules by conglutination is unlikely to have consistently increased pressure in the 2.0–2.5 mm lobar veins perfused at constant flow rates. Unpublished observations in this laboratory, using this perfusion technique, have further indicated that the pressure in these small veins is not increased by conglutination of red cells by intralobar injections of 14.5% sodium chloride solution even though lobar arterial pressure rose to 70–80 mm Hg. Additionally, the diverse pressure responses observed in the lobar artery during perfusion with blood which had been previously acidified and perfused through the femoral vascular bed and to that which had previously perfused the pulmonary vascular bed are less readily explained by conglutination. Furthermore, conglutination was not identified by Wright staining the perfused acidified blood or blood removed from cut section of the perfused lobe during acid infusions; the platelet count in the lobar vein was not decreased by acid infusions. Histological sections of the lung tissue biopsied during peak pressor responses with HCl and studied with light and electron microscopy showed no conglutination in blood vessels in the pump-perfused and normally perfused lobes. Rouleaux formation, which was present in both pump-perfused and normally perfused areas, is unlikely to have caused the localized lobar vasopressor response. Previous studies have emphasized the important rheologic differences between rouleaux formation and intravascular erythrocyte conglutination (36). Furthermore, although microscopic studies may fail to detect rapidly reversible conglutination, the peak pressor response to HCl infusions persisted for 5–10 min after cessation of the acid infusions, and only gradually returned to control pressures 10–20 min after cessation of the infusion.

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