Influence of Sympathetic Stimulation and Vasoactive Substances on the Canine Pulmonary Veins

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ABSTRACT The contribution of the intrapulmonary lobar veins to the increase in pulmonary vascular resistance in response to sympathetic stimulation was studied under conditions of controlled blood flow in the anesthetized dog in which vascular pressures were measured simultaneously in the perfused lobar artery, an intrapulmonary lobar vein 2–3 mm in diameter and in the left atrium. Stimulation of the stellate ganglia at 3, 10, and 30 cycles/s increased pressure in the lobar artery and small vein in a stimulus-related manner but decreased pressure in the left atrium. Injection of norepinephrine into the perfused lobar artery also increased pressure in the lobar artery and small vein but decreased pressure in the left atrium. The increase in lobar arterial and venous pressure in response to either injected norepinephrine or to nerve stimulation was antagonized by an alpha receptor blocking agent. The rise in pressure in both lobar artery and small vein with nerve stimulation but not administered norepinephrine was inhibited by an adrenergic nerve terminal blocking agent. These results suggest that under conditions of steady flow, sympathetic nerve stimulation increases the resistance to flow in the lung by constricting pulmonary veins and vessels upstream to the small veins, and that at each stimulus-frequency studied approximately 50% of the total increase in resistance may be due to venoconstriction. It is concluded that the increase in resistance to flow in the lung in response to nerve stimulation is the result of activation of alpha adrenergic receptors by norepinephrine liberated from adrenergic nerve terminals in venous segments and in vessels upstream to small veins, presumed to be small arteries.

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INTRODUCTION

It has been established by anatomic, histochemical, and biochemical studies in most animal species and man that the pulmonary vascular bed is innervated by the sympathetic nervous system and that transmitter is present in large quantities in canine pulmonary arteries and veins (1–6). Although the sympathetic innervation of the pulmonary vascular bed appears to be extensive, the physiologic function of the vasomotor nerves in regulating the pulmonary circulation is uncertain. In 1896, Francois-Franck showed that nerve stimulation increased pulmonary arterial pressure; however, it was not possible from these experiments to determine if the increase in pressure was due to an increase in vascular resistance or an increase in blood flow (7). Daly et al. (8–11) have demonstrated that under conditions of controlled blood flow, stimulation of the sympathetic nerves to the lung consistently increases pulmonary vascular resistance. In contrast, other investigators found little or no increase in pulmonary vascular resistance in the perfused canine lung lobe in response to sympathetic stimulation but showed that nerve stimulation decreased the distensibility of the large pulmonary arteries (12–14). In a recent study using a new right heart technique to perfuse the left lower lung lobe, we have been able to demonstrate in the dog that stimulation of the sympathetic nerves increases pulmonary vascular resistance in a stimulus-related manner (15). In addition, this response was independent of changes in respiration, bronchomotor tone, and the bronchial circulation, and the response characteristics were similar when the lobe was perfused with pulsatile or roller pumps (15). In other studies, it was shown that the increase in pulmonary vascular resistance in response to nerve stimulation, but not to injected norepinephrine, was antagonized by bretylium, an adrenergic nerve terminal blocker, whereas responses to norepinephrine and to nerve stimulation were inhibited by alpha receptor blocking agents (16). However, the site of ac-

tion of the sympathetic nerves and the relative contribution of pulmonary veins and vessels upstream to the small veins to the increase in resistance in response to nerve stimulation in the pulmonary vascular bed were not established by previous studies (8–11, 15, 16). The purpose of the present investigation was to study the effects of sympathetic nerve stimulation and of injected norepinephrine on the pulmonary lobar veins and on upstream vessels using transseptal catheterization techniques to measure pressure gradients between the perfused lobar artery, a small intrapulmonary lobar vein, and the left atrium.

METHODS

56 mongrel dogs of either sex weighing 16–24 kg and 5 beagles weighing 12–15 kg were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and were strapped in the supine position to a fluoroscopic table. A specially designed 20F balloon catheter was positioned in the artery of the left lower long lobe from the external jugular vein under fluoroscopic guidance (Philips image intensifier, Philips Electronic Instrument, Mount Vernon, N. Y.). A Teflon catheter with its tip positioned about 2 cm distal to the balloon catheter was used to measure pressure in the perfused lobar artery. Catheters with side holes were passed into the main pulmonary artery and the aorta and into a small intrapulmonary lobar vein and the left atrium transseptally. Precautions were taken to ensure that pressure measurements were made in lobar veins 2–3 mm in diameter without wedging. Briefly, a 0.9-mm Teflon catheter having side holes near its tip was passed through a 3-mm Teflon catheter that had been previously wedged in a small pulmonary lobar vein. The 0.9-mm catheter was then withdrawn 1–3 cm from the wedge position until pressure dropped abruptly. It was then fixed in place with a Cope adaptor (Becton-Dickinson and Co., Rutherford, N. J.) after the Teflon catheter had been withdrawn to the left atrium. When Hypaque (sodium diatrizoate, 50% Winthrop Laboratories, Evanston, Ill.) was injected into the 0.9-mm catheter, the contrast media returned rapidly to the left atrium. The catheter positions are shown in Fig. 1 and the methods have been described in detail (17, 18).

All vascular pressures were measured with Statham P23D transducers and mean pressures recorded on an oscilloscopic recorder, model DR-8 or DR-12 (Electronics for Medicine, Inc., White Plains, N. Y.). The middle of the right atrium was used as the zero pressure reference for all transducers. After all catheters were positioned and the animals heparinized (500 U/kg), the balloon on the perfusion catheter was distended with 2–4 ml Hypaque until pressure in the perfused lobar artery and small vein decreased to near left atrial pressure. The left lower lobe was then perfused with a Sarns roller pump (model 3,500, Sarns, Inc., Ann Arbor, Mich.) with blood withdrawn from the right atrium. The pumping rate was adjusted so that mean lobar arterial perfusion pressure approximated mean pressure in the main pulmonary artery and thereafter was not changed during the experiment. The pumping rate averaged 332 ml/min in these experiments. A standard lead II electrocardiogram was monitored on the oscilloscopic recorder. The trachea was intubated with a cuffed endotracheal tube, and the animals were ventilated with room air using a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). Mean respiratory rate was 20 cycles/min and mean stroke volume was 260 ml or about 13 ml/kg. The phase was set so that the ratio of inspiration to expiration varied from 40 to 60%. Arterial blood gases and pH in these animals were determined with a Radiometer analyzer (London Co., Cleveland, Ohio) and were pH 7.34 ±0.08, Po_2 81.5±1.4 mm Hg and Pco_2 33.7±1.3 mm Hg. In some experiments, end expiratory pressure was set at 3 cm H_2O.

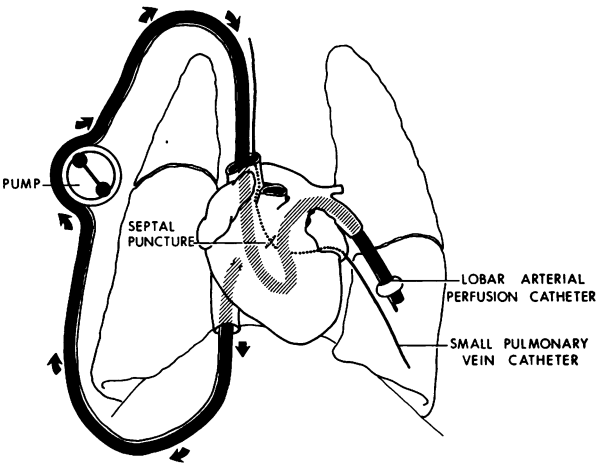

FIGURE 1 Diagram showing catheterization procedure in the dog. A specially designed 20F balloon catheter is passed into the artery of the lower left lobe and the lung is autoperfused with blood withdrawn from the right atrium. Vascular pressures are measured in the perfused lobar artery, a small pulmonary lobar vein, and the left atrium and in the main pulmonary artery and the aorta.

The left stellate ganglion was approached by way of a left thoracotomy, and the nerve was carefully isolated and placed upon a shielded Harvard Electrode. The nerve was excited with square-wave pulses, 2 ms duration supramaximal voltage (10–18V) with a Grass model S48 stimulator and isolation unit (Grass Instrument Co., Quincy, Mass.). The nerve was stimulated at 3, 10, and 30 cycles/s for periods of 30–45 s, and the frequency of stimulation was randomized. In the five beagles, a Medtronic's angiostat (Medtronic, Inc., Minneapolis, Minn.) was placed around the left stellate ganglia, and the chest was closed. Three of the animals were returned to vivarium for 10–21 days after which time they were catheterized. The other two animals were studied on the same day after the chest was closed. Norepinephrine (1-norepinephrine hydrochloride, Sigma Chemical Co., St. Louis, Mo.) and histamine phosphate (Lilly Chemical Products, Inc., Gardner, Mass.), dose in terms of base, angiotensin (Angiotensin II amide, Ciba Corp., Summit, N. J.), and $PGF_{2\alpha}$, (Upjohn Co., Kalamazoo, Mich.) dose in terms of salt, were injected directly into the lobar arterial perfusion circuit in small volumes. Phentolamine hydrochloride (Regitine, Ciba Corp.), 200–400 μg/min, and guanethidine sulfate (Ismelin, Ciba Corp.), 200 μg/min, were infused into the lobar arterial perfusion catheter in a volume calculated to achieve a rate of 0.1–0.2 ml/min with a Harvard infusion pump (Harvard Apparatus Co.). Propranolol (Inderal, Ayerst Laboratories, New York) 0.5–1 mg/kg was injected into a femoral vein over a 3–5-min period. For studies on isolated canine intrapulmonary vessels, mongrel dogs weighing 12–23 kg were anesthetized

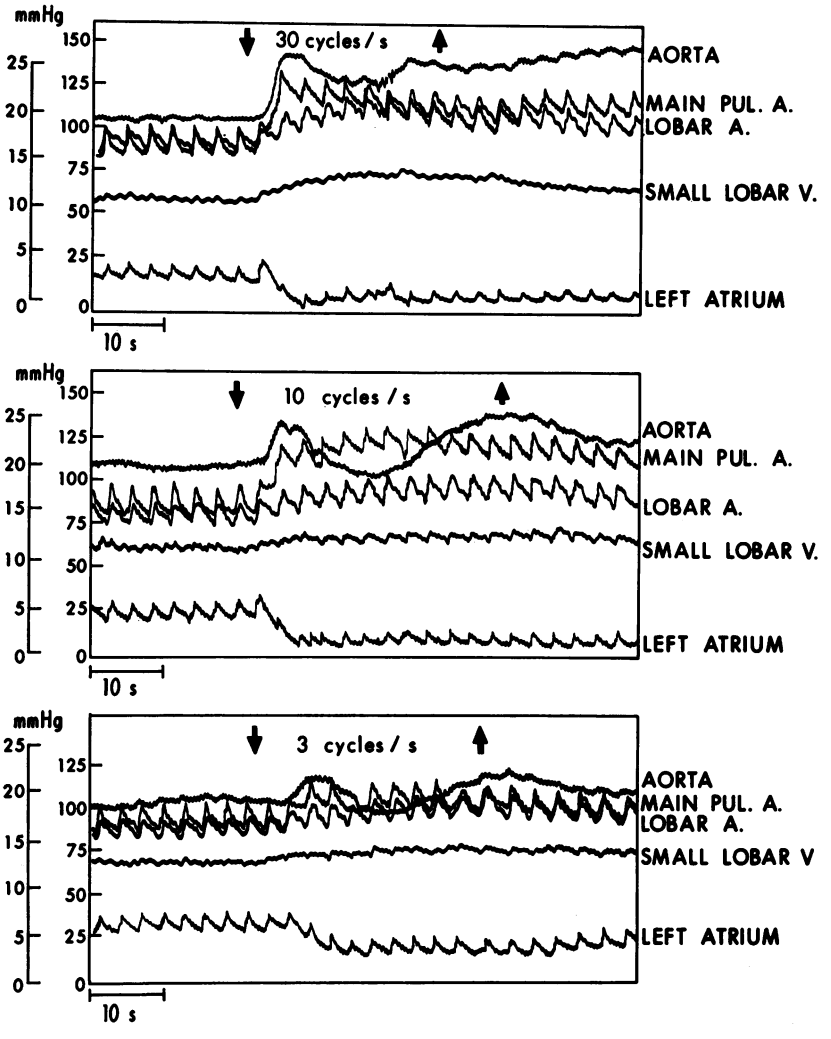

FIGURE 2 Records from an experiment showing the effects of stimulation of the sympathetic nerves at 3, 10, and 30 cycles/s on pressures in the lobar artery, small intrapulmonary lobar vein, left atrium, main pulmonary artery, and aorta in the dog.

with pentobarbital 30 mg/kg i.v. and were sacrificed by bleeding. Lung lobes were removed quickly, and segments of artery and vein 3–5 mm in diameter were isolated and carefully cleaned of surrounding tissue. The vessels were used immediately or stored overnight at 4°C in physiological salt solution. Responses to norepinephrine and other standard agonists were similar in fresh and cold stored vessels. Intrapulmonary vessels were also obtained from six patients after lobectomy for bronchogenic carcinoma. The physiologic salt solution contained 125 mM NaCl, 2.7 mM KCl, 1.8 mM $CaCl_2$, and 11 mM glucose. The solution was vigorously bubbled with 100% oxygen and buffered at pH 7.4 with HCl and Tham (Sigma Trizma base buffer, Sigma Chemical Co.) 23.8 mM. Helical segments of artery and vein 5–10 mm in width were mounted in 15-ml baths. One end of the segment was fastened to a stainless steel hook and the other to a Grass (FTO3, Grass Instrument Co.) force displacement transducer. The strips were bathed in physiologic salt solution, bubbled with oxygen, and maintained at 37°C. The stretching force was 4 g for arteries and 3 g for veins. The vessels were allowed to equilibrate for 2 h before exposure to norepinephrine. Dose response curves were determined in a cumulative manner. All data were evaluated using methods described by Snedecor and Cochran for paired and group comparisons (19). All values are presented at mean±SEM, and a P value of less than 0.05 was considered significant.

RESULTS

Sympathetic nerve stimulation. The effects of sympathetic nerve stimulation on mean vascular pressures in the dog are shown in Fig. 2, and data from 13 experiments are summarized in Table I. Stimulation of the sympathetic nerves at 3, 10, and 30 cycles/s significantly increased pressure in the lobar artery, the small intrapulmonary lobar vein, the aorta, and the main pulmonary artery and significantly decreased pressure

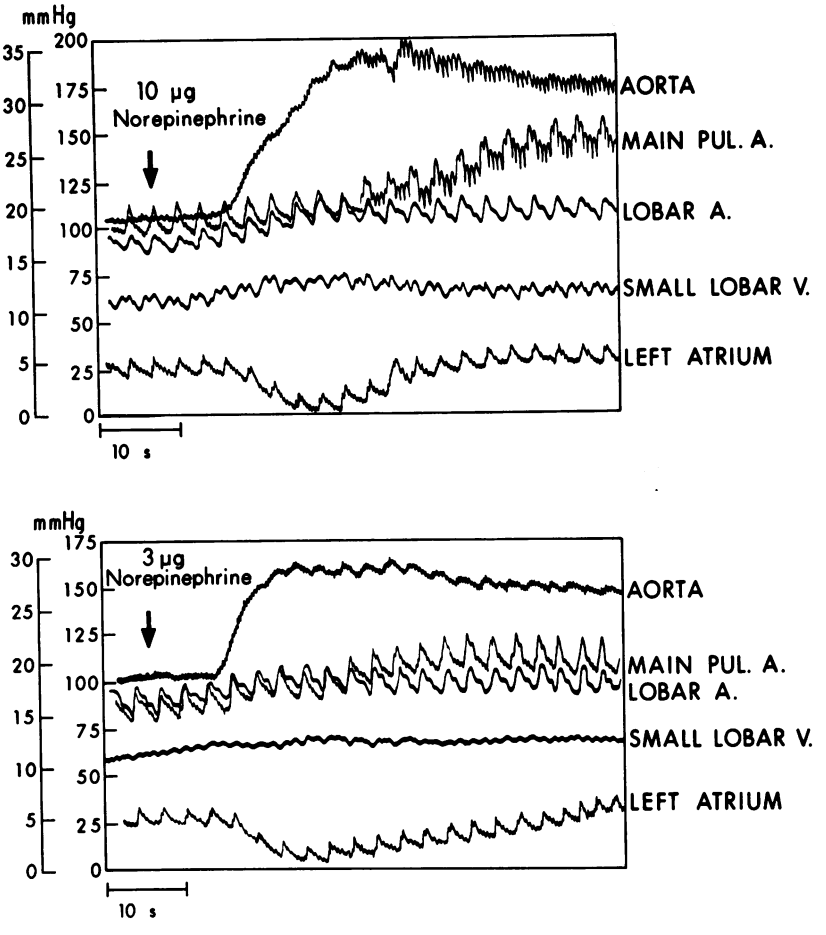

FIGURE 3 Records from an experiment showing the effects of norepinephrine injections, 3 and 10 µg, into the lobar artery on pressures in the lobar artery, small intrapulmonary lobar vein, left atrium, main pulmonary artery, and aorta in the dog.

in the left atrium. The increase in mean pressure in both lobar artery and small vein was stimulus related over the range of stimulus frequency studied, and a steady state was usually attained 20–25 s after onset of stimulation (Fig. 2 and 5). The rise in aortic pressure was not well maintained during the period of stimulation after a peak had been reached (Fig. 2). All vascular pressures returned toward control value after the stimulus was terminated. The effects of norepinephrine on vascular pressures were studied in these same dogs, and a record from one experiment is shown in Fig. 3. Injection of 3 and 10 µg norepinephrine into the perfusion circuit caused a significant increase in pressure in the lobar artery and in the small intrapulmonary lobar vein, the aorta, and the main pulmonary artery and caused a significant decrease in pressure in the left atrium (Table I). All vascular pressures returned slowly to control value, and the rise in aortic pressure was greater and more regular with norepinephrine than with nerve stimulation (Fig. 2–4). In two other dogs, the effects of norepinephrine on pressure in two small veins and a large vein were evaluated. The rise in pressure in a small vein in the apex and in the base of the left lower lobe was similar, and pressure in the large vein tended to fall with the left atrium (Fig. 4). The increases in pressure in the lobar artery and vein in response to the two doses of the sympathomimetic amine were graded, and the increments in pressure at 10 and 30 cycles/s were similar to increments at 3 and 10 µg, respectively (Fig. 5).

The effect of nerve stimulation and injected norepinephrine on mean pressure gradients across the lung in the dogs with acute electrode placement, in the present study, are summarized in Table II. Sympathetic nerve stimulation and norepinephrine injection increased the mean gradient from lobar artery to left atrium at each stimulus frequency and dose studied ($P < 0.001$). The mean increase in resistance across the left lower lobe was 25,34, and 43% at 3, 10, and 30 cycles/s and 35 and 42% at 3 and 10 µg of norepinephrine. Nerve

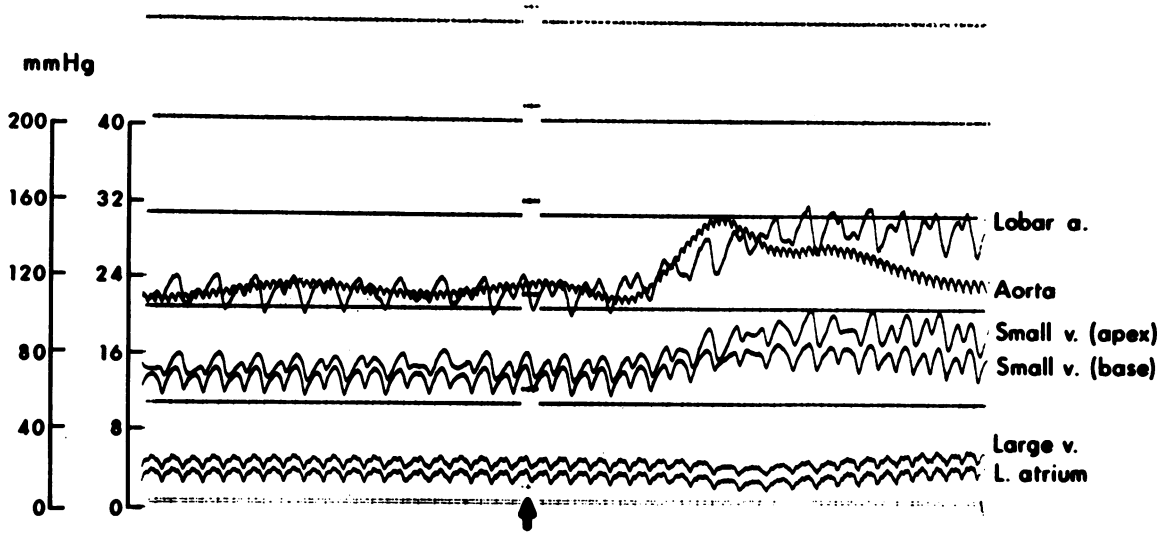

FIGURE 4 Records from an experiment showing the effect of norepinephrine, 10 μg, into the lobar artery on pressures in the aorta, lobar artery, a small vein in the apex of the lobe and one in the base, a large vein, and the left atrium.

stimulation and norepinephrine significantly increased the pressure gradient from lobar artery to lobar small vein and the gradient from lobar small vein to left atrium at each stimulus frequency and dose studied.

Blocking agents. The effects of phentolamine, an alpha receptor blocking agent, and guanethidine, an adrenergic nerve terminal blocking agent, on responses to norepinephrine and nerve stimulation were studied in two groups of dogs. In these experiments dose and frequency response curves for norepinephrine and nerve stimulation were determined in the presence and absence of the blocking agents. In the first group of dogs, responses to norepinephrine and nerve stimulation were obtained before and during infusion of phentolamine, 0.2–0.4 mg/min, directly into the perfusion circuit. During infusion of phentolamine, the rise in lobar arterial and lobar venous pressure in response to nerve stimulation and injected norepinephrine was significantly de-

TABLE I

Mean Data with Sympathetic Nerve Stimulation and Injected Norepinephrine

	Pressure				
	Lobar artery	Lobar vein	Left atrium	Aorta	Main pulmonary artery
	*mm Hg ± SEM**				
Sympathetic nerve stimulation, n = 13					
Control	21.6±1.2	13.0±1.0	6.7±0.8	82.0±5.3	18.6±2.0
3 cycles/s	23.6±1.3	14.3±1.1	5.0±0.7	95.8±5.6	20.7±2.2
Control	21.7±1.1	13.3±1.1	6.5±0.8	83.8±5.1	19.0±1.9
10 cycles/s	25.4±1.2	15.8±1.1	4.7±0.7	106.5±6.1	22.0±2.3
Control	21.3±1.1	12.9±0.9	5.9±0.8	90.3±5.2	18.6±1.8
30 cycles/s	26.3±1.3	16.5±0.8	4.1±0.9	118.1±5.8	22.8±2.3
Norepinephrine, n = 13					
Control	21.0±1.1	13.9±0.7	6.7±0.9	87.3±5.1	19.5±2.0
3 μg	23.8±1.2	16.0±0.5	4.1±1.0	120.4±5.8	22.7±2.1
Control	21.2±1.1	14.5±0.8	5.9±0.9	89.6±4.8	19.5±1.8
10 μg	24.9±1.4	17.2±0.7	2.8±1.1	136.5±8.1	24.0±2.1

* All values are significantly different from corresponding controls ($P < 0.05$, paired comparison).

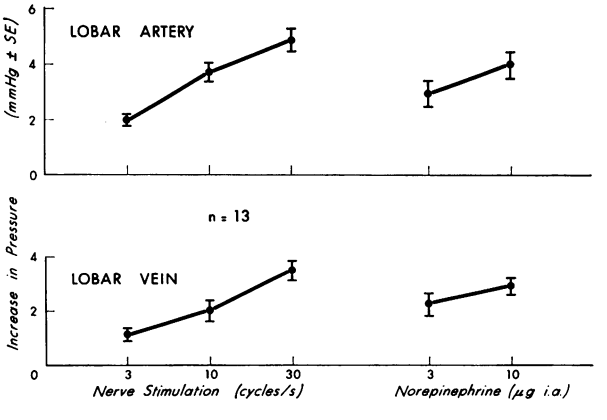

FIGURE 5 Frequency-response relationship for sympathetic nerve stimulation and dose-response relationship for norepinephrine in the left lower lung lobe; n indicates the number of dogs tested.

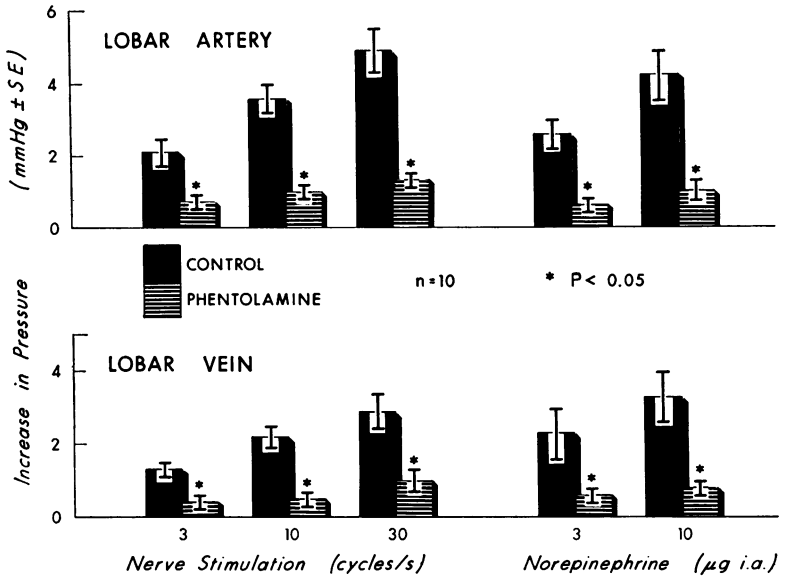

FIGURE 6 Influence of phentolamine, an alpha receptor blocking agent, on responses to sympathetic nerve stimulation and injected norepinephrine in the lobar artery and small intrapulmonary lobar vein. n indicates number of dogs tested.

creased at each dose of the sympathomimetic amine and stimulus frequency studied when compared to corresponding controls (Fig. 6). Infusion of the alpha adrenergic blocking agent significantly decreased pressure in the aorta but had no significant effect on pressure in the lobar artery, the intrapulmonary lobar vein, the left atrium, or the main pulmonary artery (Table III).

In the second group of dogs infusion of guanethidine, 0.2 mg/min, into the perfusion circuit produced a significant increase in pressure in the lobar artery, the aorta, and the main pulmonary artery. These pressures returned toward control value 20–40 min later and were not significantly different from control 50–60 min after the onset of the infusion (Table III). The rise in lobar arterial and venous pressure in response to nerve stimulation was significantly decreased at 3, 10, and 30 cycles/s when compared to corresponding control values (Fig. 7). The increase in pressure in the lobar artery and small vein in response to the 3-μg dose of norepinephrine and the increase in pressure in the lobar artery with the 10-μg dose of norepinephrine was not significantly different from control (Fig. 7). The increase in pressure in the lobar vein in response to norepinephrine, 10 μg, was significantly greater than control during infusion of the nerve terminal blocking agent (Fig. 7).

The effects of saline infusion and passage of time on responses to norepinephrine and nerve stimulation were evaluated in another series of animals. The increase in lobar arterial and lobar venous pressure in response to nerve stimulation and injected norepinephrine was not significantly different when compared to control value 30–60 min after onset of infusion of physiologic saline, 0.1–0.2 ml/min, the vehicle for the adrenergic blocking agents (Fig. 8). Infusion of this amount of saline into

TABLE II

Influence of Sympathetic Nerve Stimulation and Injected Norepinephrine on Mean Pressure Gradients in the Lung

	Pressure gradient		
	Lobar artery Left atrium	Lobar artery Lobar vein	Lobar vein Left atrium
	*mm Hg±SEM**		
Nerve stimulation, n = 36			
Control	15.6±0.9	7.9±0.7	7.8±0.7
3 cycles/s	19.6±0.7	8.8±0.8	10.8±0.7
Control	15.8±0.8	8.3±0.7	7.6±0.7
10 cycles/s	21.5±0.9	9.8±0.7	11.6±0.7
Control	15.9±0.8	8.0±0.6	7.6±0.6
30 cycles/s	22.5±0.9	10.0±0.7	12.8±0.6
Norepinephrine, n = 36			
Control	15.5±0.8	7.1±0.7	8.4±0.7
3 μg	21.1±1.6	8.1±0.7	12.9±0.7
Control	15.7±0.9	6.5±0.8	9.2±0.7
10 μg	22.9±1.1	7.7±0.8	15.2±0.9

* All gradients are significantly different from corresponding controls ($P < 0.001$, paired comparison).

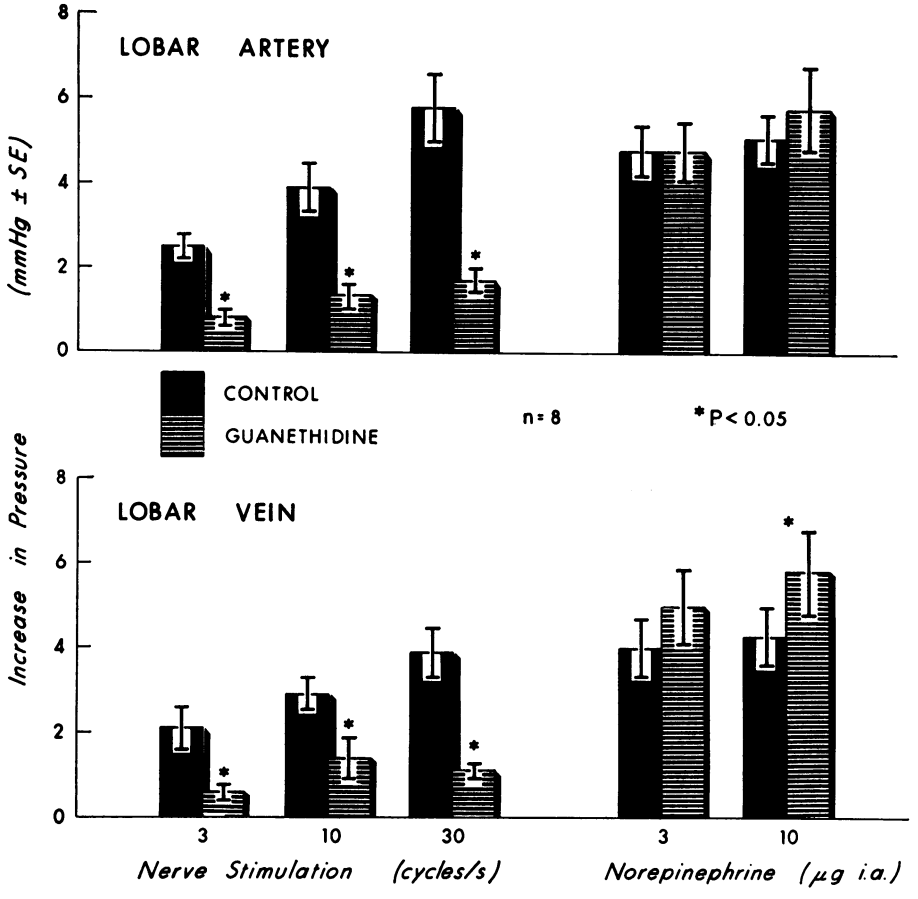

FIGURE 7 Influence of guanethidine, an adrenergic nerve terminal blocking agent, on responses to sympathetic nerve stimulation and injected norepinephrine in the lobar artery and small vein. n indicates number of dogs tested.

the perfusion circuit did not significantly alter pressure in the lobar artery, the small vein, the left atrium, the main pulmonary artery, and the aorta (Table III).

Nerve stimulation in the intact animal. The effects of nerve stimulation on mean vascular pressures in the lung were studied in five intact, spontaneously breath-

TABLE III

Mean Data with Infusions of Phentolamine, Guanethidine, and Saline

	Pressure				
	Lobar artery	Lobar vein	Left atrium	Aorta	Main pulmonary artery
			mm Hg±SEM		
Control	20.8±1.3	14.2±1.0	6.2±0.8	88.5±3.3	17.5±1.1
Phentolamine, n = 10	19.6±1.5	13.2±1.1	4.8±0.6	73.5±4.3*	16.6±0.9
Control	28.5±1.6	17.3±1.9	5.1±0.6	86.9±5.7	17.6±1.6
Guanethidine, n = 8	30.0±1.7	16.5±2.0	5.0±0.5	82.5±5.5	18.5±1.5
Control	20.2±1.0	14.4±0.7	4.8±0.7	82.0±13.0	15.8±1.6
Saline, n = 5	20.8±1.6	13.6±0.9	4.7±0.6	79.5±10.2	16.2±1.7

* Significantly different from corresponding control ($P < 0.05$, paired comparison).

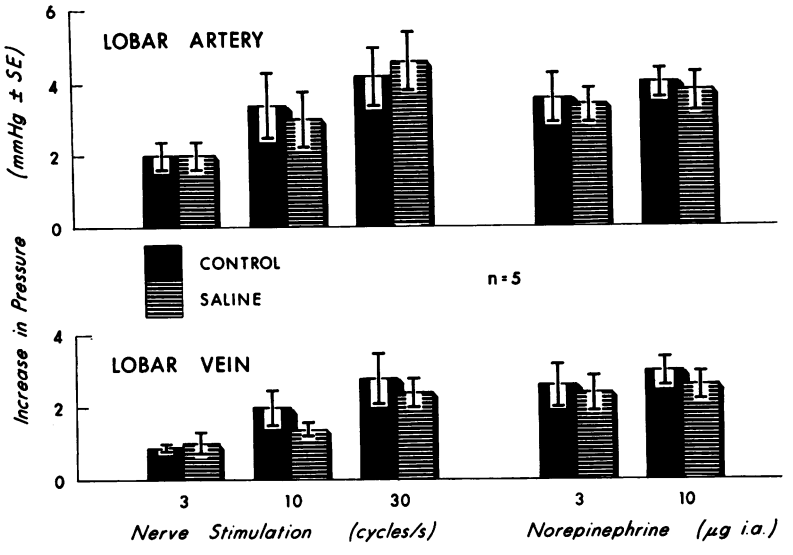

FIGURE 8 Effects of isotonic saline infusion (0.1–0.2 ml/min) on responses to sympathetic nerve stimulation and injected norepinephrine in the lobar artery and small vein. n indicates number of dogs tested.

ing beagles. The results of these studies are summarized in Table IV. Stimulation of the sympathetic nerves significantly increased pressure in the lobar artery and lobar small vein in the intact animals. In three experiments, the stimulating electrode was implanted 10–21 days beforehand so that thoracotomy was avoided, and in two other experiments the chest was closed acutely. There was a trend for left atrial pressure to decrease during nerve stimulation; however, the change was not statistically significant. Injection of 3 and 10 μg norepinephrine also significantly increased pressure in the lobar artery and lobar small vein.

Relationship between aortic pressure and pressure in the perfused lobar artery and small vein. Distension of a balloon catheter in the aorta at the level of the diaphragm increased aortic pressure from 140 to 210 mm Hg but caused little if any change in pressure in the perfused lobar artery or small vein (Fig. 9, middle panel). Distension of the balloon catheter in the proximal portion of the aorta decreased pressure in the thoracic aorta from 140 to 20 mm Hg but had little or no effect on pressure in the lobar artery or small vein (Fig. 9, right panel). Injection of norepinephrine into the root of the aorta increased aortic pressure from 140 to 200 mm Hg but produced little change in pressure in the lobar artery or small vein (Fig. 9, left panel).

The rise in aortic pressure and the fall in left atrial pressure during nerve stimulation and norepinephrine administration probably results from the effect of catecholamines on cardiac contractility. Inasmuch as the actions of catecholamines on contractility are mediated by beta receptors, the effects of propranolol, a beta blocker, were evaluated. In a group of six dogs the fall in left atrial pressure in response to norepinephrine was completely abolished, whereas the rise in aortic pressure was decreased significantly and slower in onset after propranolol (Fig. 10, Table V). However, the rise in pressure in the perfused lobar artery and small vein was not changed (Fig. 10, Table V).

TABLE IV

Mean Data with Sympathetic Nerve Stimulation and Injected Norepinephrine in the Spontaneously Breathing Beagle

	Lobar artery	Lobar vein	Left atrium
		mm Hg±SEM	
Sympathetic nerve stimulation, $n = 5$			
Control	17.8±1.6	10.3±1.1	0.8±0.2
3 cycles/s	19.3±1.8*	11.3±1.1*	−1.3±0.4
Control	20.0±1.6	10.6±0.9	1.2±0.8
10 cycles/s	22.5±1.7*	12.2±1.1*	−0.2±0.9
Control	20.0±1.6	11.0±1.2	1.6±0.8
30 cycles/s	23.2±1.4*	13.1±1.2*	0.0±0.9
Norepinephrine, $n = 5$			
Control	18.2±1.2	11.6±1.3	1.6±0.8
3 μg	21.4±1.1*	13.2±1.3*	0.0±0.9
Control	19.6±1.2	11.6±1.6	1.4±1.0
10 μg	23.2±1.4*	14.0±1.7*	1.0±1.1

* Significantly different from corresponding control ($P < 0.05$, paired comparison).

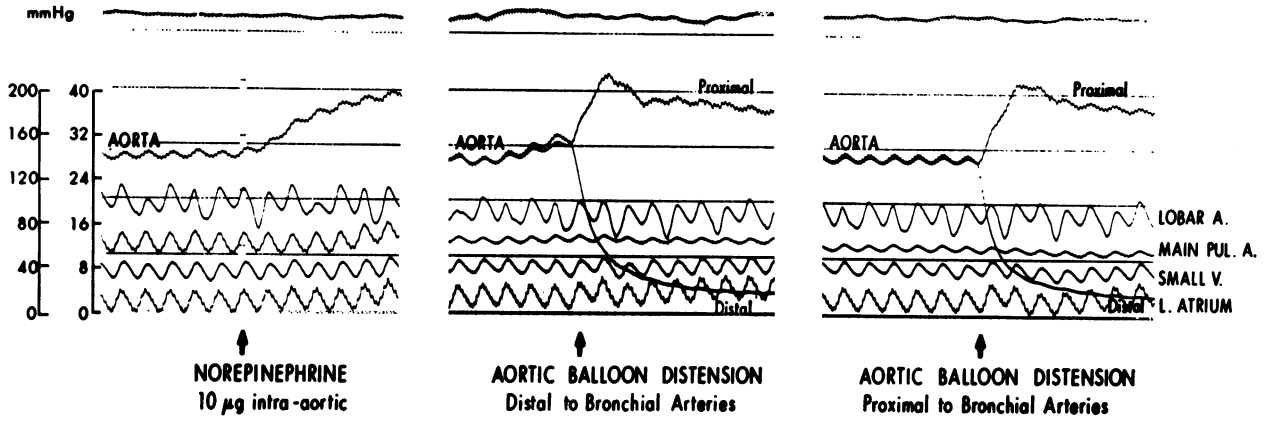

FIGURE 9 Left panel, record showing the effect of intra-aortic norepinephrine on vascular pressures in dog. Middle panel, effect of distension of a balloon catheter in the aorta at the level of the diaphragm on pressures in the dog. Right panel, effect of distension of a balloon catheter in the proximal portion of the aorta on vascular pressures in the dog.

In other experiments the effects of angiotensin, histamine, and prostaglandins $F_{2\alpha}$ ($PGF_{2\alpha}$) on vascular pressures in the dog were evaluated. Injection of angiotensin into the lobar artery increased pressure in the lobar artery, left atrium, and aorta but did not affect pressure in the small vein or main pulmonary artery (Table VI). Histamine increased pressure in the lobar artery and small vein, decreased pressure in the aorta, but did not affect pressure in the main pulmonary artery or the left atrium (Table VI). $PGF_{2\alpha}$ increased lobar arterial and venous pressure but did not affect pressure in the aorta, the main pulmonary artery, or the left atrium (Table VI).

Isolated canine and human intrapulmonary vessels. Norepinephrine increased isometric tension in isolated helical segments of intrapulmonary lobar artery and

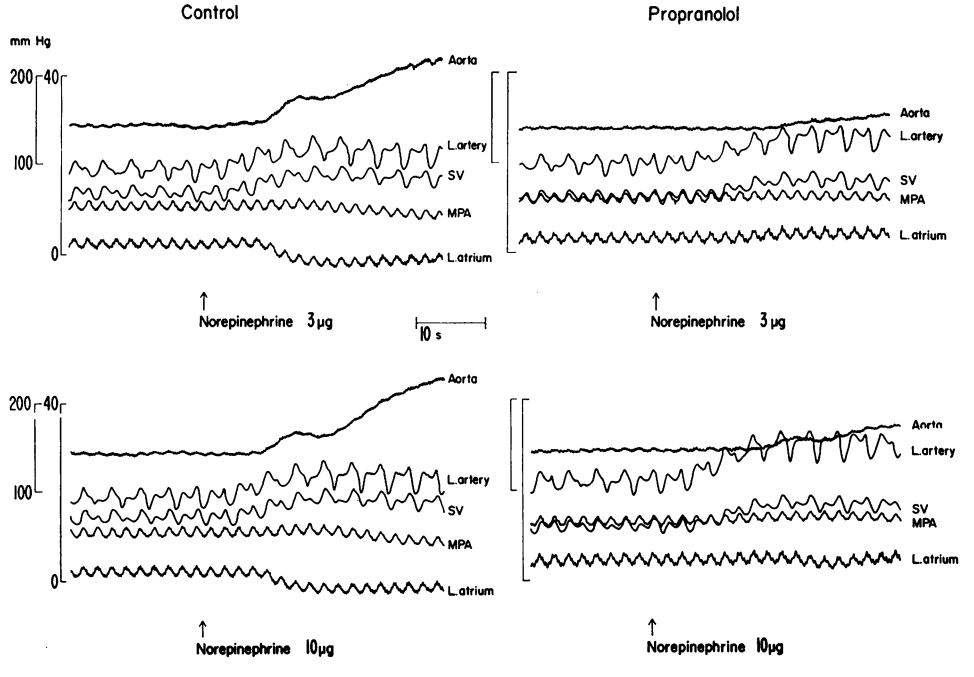

FIGURE 10 Records from an experiment showing the effect of norepinephrine, 3 and 10 μg, into the lobar artery on pressures in the aorta, lobar artery (L artery), small lobar vein (SV), main pulmonary artery (MPA), and left atrium (L atrium) before and after administration of propranolol, 0.5–1 mg/kg i.v.

TABLE V
Responses to Norepinephrine before and after Propranolol

	Pressure				
	Lobar artery	Lobar vein	Left atrium	Aorta	Main pulmonary artery
	mm Hg±SEM				
Before propranolol					
Control	20.7±1.1	11.5±1.2	2.8±0.5	110±7	15.3±2.2
3 μg	24.3±1.0*	13.8±1.4*	0.3±0.9*	153±3*	16.5±2.5
Control	20.2±1.2	11.5±1.1	3.2±0.4	111±7	14.8±1.8
10 μg	25.2±1.0*	14.8±1.6*	0.5±0.7*	169±13*	16.7±2.2*
After propranolol, 0.5 − 1 mg/kg i.v.					
Control	20.5±1.2	11.4±0.6	3.7±0.5	105±10	13.0±1.0
3 μg	25.0±1.3*	14.0±0.7*	4.2±0.5	122±10*	14.7±1.1
Control	20.8±1.1	11.3±0.9	4.0±0.7	104±10	13.0±1.4
10 μg	27.0±1.7*	14.7±0.9*	4.3±0.6	123±11*	14.8±1.5

* Significantly different from corresponding control ($P < 0.05$), $n = 6$.

vein from canine and human lung (Fig. 11 and 12). In canine vessels concentrations of norepinephrine from 10^{-8} to 10^{-5} M resulted in a dose-related increase in isometric tension (Fig. 11). Wall thickness for the arterial segments was 0.46±0.03 mm and 0.27±0.01 mm for veins. The difference in wall thickness was significant. In six human arteries the increases in tension with norepinephrine 10^{-6}–10^{-5} M, and 127 mM K^+ were 1.09±0.25, 1.37±0.30, and 1.41±0.18 g. In six veins from human lung these increases were 0.32±0.06, 0.63±0.19, and 1.88±0.30 g.

TABLE VI
Influence of Angiotensin, Histamine, and $PGF_{2\alpha}$ on Mean Vascular Pressures in the Dog

	Lobar artery	Lobar vein	Left atrium	Aorta	Main pulmonary artery
	mm Hg±SEM				
Angiotensin, $n = 5$					
Control	20.0±1.7	9.4±0.4	2.6±0.9	120±6	12.8±0.7
3 μg	23.7±1.7*	9.5±0.5	4.0±0.9*	149±8*	13.0±0.8
Control	20.4±1.3	10.6±1.3	2.2±0.7	120±7	12.4±0.9
10 μg	25.8±1.5*	10.8±1.1	3.8±0.7*	163±6*	12.2±0.8
Histamine, $n = 4$					
Control	20.3±2.3	9.8±1.8	1.8±0.2	124±7	12.6±1.1
10 μg	22.8±2.9*	13.0±1.6*	1.0±0.8	91±6*	13.6±1.2
Control	20.5±2.4	10.3±2.1	1.5±0.3	126±8	12.6±0.9
30 μg	24.8±3.7*	14.5±2.1*	0.8±0.7	77±6*	13.6±1.2
$PGF_{2\alpha}$, $n = 7$					
Control	21.1±1.3	13.0±0.9	2.6±0.3	129±8	18.1±1.7
0.3 μg	25.7±1.7*	16.0±1.3*	2.3±0.5	129±7	18.3±1.5
Control	20.3±1.1	14.4±0.4	2.3±0.3	123±7	18.0±1.5
1.0 μg	25.9±1.6*	18.0±0.9*	2.1±0.3	122±7	18.3±1.7

* Significantly different from corresponding control ($P < 0.05$).

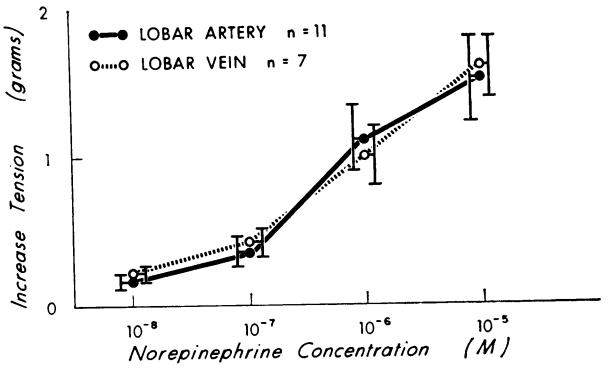

FIGURE 11 Effect of norepinephrine on isometric tension output in isolated helical segments of canine intrapulmonary lobar artery and vein 3–5 mm in diameter. Norepinephrine dose response curves were determined in a cumulative manner.

DISCUSSION

Results of the present study show that sympathetic stimulation increases the pressure gradient across the canine lung lobe. Inasmuch as blood flow was constant and left atrial pressure did not rise, the increase in gradient represents an increase in resistance to flow in the lung. Resistance rose 25, 34, and 43% in the open chest dog at 3, 10, and 30 cycles and was similar in the intact beagle. The increase in resistance was similar in the present study and in a previous study although different anesthetics were used (15). The increase in resistance at 30 cycles/s was comparable to the increase at 47 cycles/s in the studies of Daly, Ramsay, and Waaler (11). Results of the present study extend previous findings by showing that the increase in pulmonary resistance was associated with a stimulus-related increase in pressure in small intrapulmonary veins.

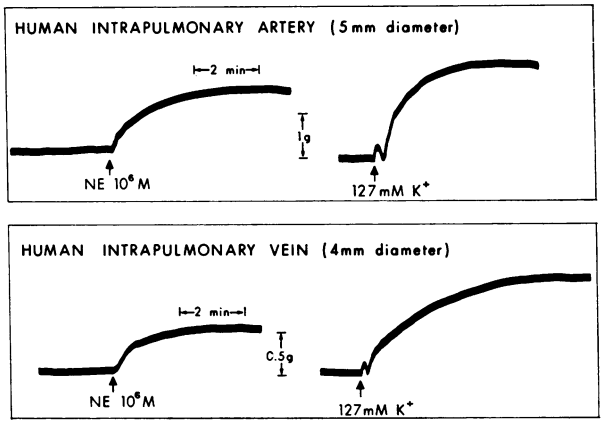

FIGURE 12 Effects of norepinephrine and high potassium on isometric tension output of human intrapulmonary lobar artery and vein. Norepinephrine and 127 mM K^+ were added to the bath at the arrow.

These data suggest that the increase in pulmonary resistance in response to nerve stimulation may be mediated in part by constriction of pulmonary veins. Norepinephrine also increased pulmonary vascular resistance and pressure in small intrapulmonary veins, and with both stimuli the rise in venous pressure was consistent even though different representative veins 2–3 mm in diameter were studied.

The rise in lobar arterial and venous pressure in response to nerve stimulation and norepinephrine was probably not related to coincident changes in aortic pressure since large changes in aortic pressure produced by balloon distension or intra-aortic norepinephrine had little effect on pressures in the lobe. Experiments with vasoactive substances also support this conclusion. For example, it is possible to observe an increase in lobar arterial and venous pressure in experiments in which aortic pressure was increased (norepinephrine, Table I), aortic pressure was unchanged ($PGF_{2\alpha}$, Table VI), or aortic pressure was decreased (histamine, Table VI). In contrast, an agent such as angiotensin that acts predominantly on arterial segments increased lobar arterial pressure in the absence of a change in pressure in the small vein even though aortic pressure increased markedly (Table VI). These data indicate that large changes in aortic pressure have little effect on pressure in the perfused lobar artery or small vein. These results suggest that changes in bronchial inflow or bronchopulmonary shunt flow are of limited importance when compared to the direct effects of these agents on pulmonary veins or upstream vessels. The present data are not inconsistent with studies showing that bronchial flow is only a small percentage of lobar flow and that large changes in aortic pressure produced only small inconsistent changes in perfusion pressure in the lung (9). The rise in venous pressure was similar after the fall in left atrial pressure in response to norepinephrine was blocked by propranolol. These data indicate that the rise in venous pressure was not due to passive constriction in the venous segments. The increases in lobar arterial and venous pressure were similar after propranolol although the rise in aortic pressure was smaller and slower in onset. Hence, baroreceptor reflexes are probably of minor importance in this response.

The increase in gradient from lobar artery to small vein and from small vein to left atrium suggests that resistance to flow is increased in venous segments and in vessels upstream to small veins presumed to be small arteries.

Results of studies on isolated vessels show that both canine and human intrapulmonary veins are responsive to norepinephrine. In fact, canine veins generate nearly twice as much active tension per unit cross-sectional area as arteries of the same size. These data indicate that veins 3–5 mm in diameter may undergo a significant decrease in cross-sectional area when exposed to either exogenous or neurogenically released norepinephrine.

The rise in lobar arterial and venous pressure in response to nerve stimulation and norepinephrine could be blocked by phentolamine, an alpha receptor blocking agent. These data indicate that these responses are mediated by alpha receptors in the veins and upstream vessels. In contrast, the rise in lobar arterial and venous pressure in response to nerve stimulation, but not to norepinephrine, was blocked by guanethidine, an adrenergic nerve terminal blocking agent. These results indicate that the rise in lobar arterial and venous pressure is the result of release of norepinephrine from adrenergic nerve terminals in venous segments and upstream vessels. The responses of the pulmonary vascular bed to nerve stimulation and norepinephrine was consistent in a large group of dogs, and these responses were reproducible with respect to time and were not altered by administration of the saline vehicle for the adrenergic blocking agents.

The validity of small vein pressure as an indicator of downstream venous resistance may be questioned if flow is inconstant in the vein in which the 0.9-mm catheter is placed. However, changes in venous pressure were similar in other representative vein 2–3 mm diameter in the lobe and changes in bronchial flow induced by large changes in aortic pressure had little if any effect on venous pressure. It is possible that during venous constriction the catheter may create a "critical" resistance as cross-sectional area of the vessel decreases. Although a critical decrease in cross-sectional area may tend to overestimate the increase in resistance, whereas an increase in flow velocity may tend to underestimate the observed response, these changes are nevertheless indicative of an active change in vessel caliber. However, the small catheter occupies less than 20% of the cross-sectional area of the vessel and since resistance is inversely related to fourth power changes in diameter, only small decreases in caliber are needed to produce the resistance changes observed in this study. In addition, changes in velocity would tend to have only small effects on lateral pressure measured through side holes in the small vein catheter. Adrenergic interventions increase cardiac output, and large increments in flow in the naturally perfused lungs may increase pressure in the vein draining the left lower lobe. However, the fall in left atrial pressure and the decrease in pressure in the large vein indicate that increments in flow in naturally perfused lobes do not raise pressure in large veins in the pump perfused lobe. In addition, propranolol blocks the effects of catecholamine stimulation

on the heart but does not affect the increase in lobar arterial and venous pressure in response to norepinephrine. Furthermore, the left lower lobe in the dog is drained by a single large vein which enters the left atrium without communicating with other veins (20).

Although it has been reported that the canine pulmonary veins are innervated by the sympathetic nervous system, the effects of nerve stimulation have not to our knowledge been documented before. The effects of nerve stimulation on calculated extrapulmonary venous resistance have been studied by Eliakim and Aviado (21) who reported that stimulation elicited modest increases in calculated extrapulmonary venous resistance in three dogs. However, absolute changes in venous pressure were not reported (21). Results of the present study are consistent with the studies of Stern and Braun who reported that chemoreceptor stimulation and hypothermia were found to reflexly increase pulmonary venous resistance, and that these effects are mediated by the sympathetic nervous system (22, 23). The results of Stern and Braun along with the present data suggest a use for adrenergic blocking agents in clinical conditions in which sympathetic activity my be heightened, such as pulmonary edema or pulmonary hypertension (22, 23).

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