Effect of Sympathetic Nerve Stimulation on Pulmonary Vascular Resistance in the Dog

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ABSTRACT

The effect of sympathetic nerve stimulation on the pulmonary circulation was studied in a hemodynamically separated dog lung in which blood flow was maintained constant with a pump. Electrical stimulation of the stellate ganglia at 3, 10, and 30 cps produced a significant increase in mean lobar arterial perfusion pressure. Since lobar blood flow and left atrial pressure did not change during nerve excitation, the increase in lobar arterial pressure reflected an increase in vascular resistance across the lung. The increase in pulmonary vascular resistance was dependent on the stimulus frequency, and the time from the onset of stimulation to the attainment of the peak response was inversely related to the stimulus frequency. The response to nerve stimulation was decreased by alpha-receptor blocking agents. Lobar perfusion with a roller pump had an effect similar to perfusion with a piston pump. The response to nerve stimulation was independent of changes in rate, rhythm, and volume of respiration, changes in aortic blood pressure, and changes in airway resistance. The effects of stellate stimulation and of injected norepinephrine on vascular resistance were similar in the hemodynamically separated lobe. In essence, sympathetic nerve stimulation produced an active increase in vascular resistance in the pulmonary circulation, and the contribution of passive factors such as changes in respiration, bronchomotor tone, and bronchial circulation was minimal. Since the response was blocked by phentolamine, the increase in pulmonary vascular resistance in response to nerve stimulation was attributed to activation of alpha receptors in the pulmonary vascular bed by neurally released norepinephrine. These results demonstrate that pulmonary vascular resistance can be increased at stimulus frequencies in the physiological range of discharge for the sympathetic nervous system.

KEY WORDS stellate ganglia norepinephrine passive factors pulmonary vascular bed phentolamine pulsatile pump active vasoconstriction neurally released norepinephrine

Anatomical and histochemical studies indicate that in most species the pulmonary vascular bed is innervated by the autonomic nervous system (1, 2). However, the role of the autonomic nervous system in the regulation of the pulmonary circulation is not well understood. As early as 1896, Francois-Franck (3) showed that stimulation of the thoracic sympathetic nerves resulted in an increase in pulmonary arterial pressure; however, his studies did not indicate whether the increase in pressure was due to an increase in pulmonary vascular resistance or to an increase in pulmonary blood flow. To exclude the effect of changes in blood flow, the response of the pulmonary vascular bed to stellate stimulation was evaluated in dog lung with controlled blood flow.

Daly and co-workers (4) used such a preparation to demonstrate that stellate nerve stimulation increased pulmonary arterial pressure when blood flow was constant. Furthermore, they showed that the response of the pulmonary circulation to sympathetic nerve stimulation was independent of changes in respiration, bronchomotor tone, or bronchial circulation, and they concluded that the increase in pressure was due to active vasoconstriction in the pulmonary vascular bed (5-7). In contrast, Ingram and co-workers (8) reported that stimulation of the sympathetic nerves decreased the distensibility of the large pulmonary arteries and the precapillary bed but did not increase the calculated vascular resistance of the isolated dog lobe perfused in situ with a pulsatile pump. In support of their conclusion a report by Szidon and Fishman (9) showed that hypothalamic stimulation increased the pulse wave velocity and the elastic modulus and decreased the compliance but did not change the calculated vascular resistance. Furthermore, stellate stimulation and carotid occlusion decreased the
The pressure-diameter slope of the pulmonary artery (10, 11).

The purpose of the present study, which used a new right heart technique, was to evaluate the effects of sympathetic nerve stimulation and of injected norepinephrine on the pulmonary circulation in a hemodynamically separated lobe in which blood flow was maintained constant with a pump. We avoided procedures such as dissection of the lung and cannulation of the lobar vessels which might interfere with the innervation of the pulmonary vascular bed.

Methods

Twenty-three mongrel dogs of either sex (16—22 kg), anesthetized with urethane (1.0 g/kg, iv) or sodium pentobarbital (30 mg/kg, iv), were strapped to a fluoroscopic table. A specially designed 20F balloon catheter was introduced under fluoroscopic control from the left external jugular vein into the artery of the lower left lobe (Fig. 1). A Teflon catheter 0.9 mm in diameter with its tip positioned about 2 cm from the tip of the balloon catheter was used to measure pressure in the lobar artery. Catheters with side holes were introduced into the main pulmonary artery and the femoral artery and into the left atrium transeptally. An 18F polyethylene catheter with side holes was introduced from the right external jugular vein, passed transeptally, and positioned in the left atrium. This catheter was used to withdraw blood from the left atrium to maintain left atrial pressure constant during sympathetic nerve stimulation. Systemic injections were made through a catheter in the femoral vein. All pressures were measured with Statham P23D transducers and recorded on an oscillographic recorder. Mean pressures were obtained from the pulsatile signal by electrical averaging. The techniques used in these experiments have been described previously (12).

After all catheters were positioned and the dogs were heparinized (300 units/kg), the balloon on the perfusion catheter was distended with 2—4 ml of Hypaque until the pressure in the lobar artery decreased nearly to left atrial pressure. The lobe was perfused using a specially calibrated Sarns pump.

Diagram showing the placement of the lobar artery perfusion catheter in the dog. The balloon catheter is introduced from the left external jugular vein into the artery of the lower left lobe under fluoroscopic control. The lobe is perfused with blood from the femoral artery or the right atrium.
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(model 3500) with blood from the femoral artery or the right atrium or using a Harvard pump (model 1421) with blood from a femoral artery reservoir circuit. Responses to stellate stimulation were not different ($P > 0.3$) when the lobe was perfused with blood from the femoral artery or from the right atrium. A standard lead II electrocardiogram was monitored on the oscillographic recorder. The dogs were ventilated with a Harvard respirator through a cuffed endotracheal tube using room air enriched with oxygen. The left stellate ganglion was approached through a left thoracotomy, and the nerve was carefully isolated and placed on a shielded Harvard electrode. The nerve was stimulated with square-wave pulses, 2 msec long, 10-18 v, for 30-45-second periods with a Grass stimulator (model S48). The stimulus was isolated from ground with a Grass isolation unit, and the frequency of stimulation was randomized. Responses to nerve stimulation were obtained with the respirator stopped during expiration (30-45 seconds) and during phasic respiration at a rate of 12-20 cycles/min. Responses to nerve stimulation were similar whether the nerves were stimulated when the respirator was stopped during expiration or when respiration was phasic. In three additional dogs, a large Carlens endotracheal tube that permitted the left lower and the right lungs to be ventilated separately with two Harvard respirators was inserted. In these experiments, airway pressure in the left lung was monitored from a lateral tap during nerve stimulation, and the positions of the tracheal occlusions were confirmed fluoroscopically and at autopsy. In experiments in which the effect of changes in blood flow were studied, flow was increased by rapidly increasing the rate of the piston pump from 60, 70, or 75 cycles/min to 100, 110, or 112 cycles/min, respectively, at a constant stroke volume of 5 ml/min with a systolic cycle ratio of 1:2. In representative experiments in which the lobe was examined at autopsy, signs of pulmonary edema were absent. Norepinephrine injections (l-norepinephrine hydrochloride) were made directly into the perfusion circuit in small volumes (3 and 10 µg in 0.03 and 0.10 ml). Phentolamine (15 mg) was infused into the lobar artery over a 5-minute period after control responses were obtained in experiments in which the influence of the alpha-blocking agent was evaluated. The hemodynamic data were evaluated using methods described by Snedecor for paired and group comparisons and by a linear regression analysis (13, 14). All values are means ± se, and $P < 0.05$ was significant.

**Results**

The influence of sympathetic nerve stimulation on vascular pressures in the hemodynamically separated, perfused lobe is illustrated in Figure 2, and results from 23 experiments are summarized in Figure 3. Electrical excitation of the left stellate ganglia at 3, 10, and 30 cps increased mean lobar arterial pressure significantly. Since blood flow and left atrial pressures were unchanged during stimulation, the increase in lobar arterial pressure reflected
an increase in vascular resistance across the lung. The magnitude of the response to sympathetic stimulation was directly dependent on the stimulus frequency, whereas the latent period and the rate at which pressure rose were inversely related to the stimulus frequency. The time from the onset of stimulation to the attainment of the peak rise in pressure was 26 ± 2, 18 ± 2, and 12 ± 1 seconds at 3, 10, and 30 cps, respectively. The response was well maintained at all stimulus frequencies during the period of stimulation after the steady-state pressure was reached; perfusion pressure returned toward the control value when the electrical stimulation was terminated. There was no correlation between the rate of blood flow in the pulmonary vascular bed and the response to nerve stimulation at 30 cps over a wide range of flow in 23 individual experiments (Fig. 4, correlation r = 0.14, P > 0.1).

The response of the pulmonary vascular bed to nerve stimulation was not related to the characteristics of the pump used for lobar arterial perfusion (Fig. 5). In 18 experiments with the Sarns roller pump the responses to nerve stimulation at 10 and 30 cps were 2.6 ± 0.5 and 4.2 ± 0.3 mm Hg, respectively, and in 5 experiments with the Harvard piston pump the responses at these frequencies were 2.2 ± 0.5 and 4.4 ± 0.4 mm Hg. Further studies in three dogs in which the piston pump was used demonstrated that the response to nerve stimulation was not related to flow rate, since an increase in flow rate from an average of 340 ml/min to 530 ml/min caused no change in the response to sympathetic nerve stimulation at 30 cps.

No systematic difference in the response to nerve stimulation was observed when the dog was passively ventilated or when respiration was halted abruptly in expiration during the period of stimulation (30-45 seconds). In three experiments with separate ventilation of the left lower lobe bronchus, airway pressure at constant volume flow was unchanged by sympathetic nerve stimulation.

The change in mean aortic blood pressure during stellate nerve stimulation was inconsistent; pressure increased in 8 experiments, decreased in 11, and was unchanged in 4 others. In some experiments, biphasic responses were seen. Marked decreases in aortic blood pressure were usually associated with
the appearance of ventricular tachycardia. However, the pressure changes with nerve stimulation in the main pulmonary artery were more consistent: at 30 cps, pressure increased 3.6 ± 0.3 mm Hg in 17 dogs, was unchanged in 2 dogs and decreased slightly in 4 dogs.

The effect of phentolamine, an alpha-blocking agent, on the response of the pulmonary vascular bed to sympathetic nerve stimulation was examined in four experiments. Infusion of phentolamine (15 mg) directly into the perfusion circuit over a 5-minute period with the Harvard infusion pump resulted in a marked decrease in the aortic blood pressure but little or no change in the left atrial, the lobar arterial, or the main pulmonary arterial pressures: control pressures were 98 ± 6, 4 ± 1, 21 ± 2, and 22 ± 1 mm Hg, respectively, and after phentolamine they were 69 ± 3, 4 ± 1, 20 ± 2, and 20 ± 1 mm Hg, respectively. The response to sympathetic nerve stimulation was decreased significantly at 10 and 30 cps after the administration of phentolamine (Fig. 6); the response to a 3-μg bolus injection of norepinephrine was also decreased from 4 to 0.5 mm Hg after treatment with the alpha-blocking agent.

Earlier studies suggested that responses to nerve stimulation might be greater when the bronchial circulation is intact (6), since transfer of blood from the bronchial to the pulmonary circulation might occur during sympathetic nerve excitation. To evaluate this possibility, responses to nerve stimulation when the aortic blood pressure was normal were compared with responses when the aortic blood pressure was reduced nearly to the pressure level in the lobar artery. Reduction of aortic blood pressure was accomplished by inducing ventricular fibrillation with high-frequency stimulation using an electrode catheter positioned in the right ventricle. In six dogs, the response to nerve stimulation at 30 cps was 4.3 ± 0.6 mm Hg during the control period (aortic blood pressure 85 ± 2 mm Hg) and 3.5 ± 0.5 mm Hg during the period of ventricular fibrillation (aortic blood pressure 25 ± 4 mm Hg). These responses were not statistically different. The response of the hemodynamically separated lobe to injected norepinephrine was similar to the response to stellate stimulation. Injections of norepinephrine (3 and 10 μg) resulted in a significant dose-related increase in lobar arterial pressure (Fig. 7). This amount of norepinephrine produced a significant increase in systemic
arterial and main pulmonary arterial blood pressures.

Discussion

Electrical stimulation of the sympathetic nerves to the lung significantly increased perfusion pressure in the hemodynamically separated, perfused dog lung. Since lobar arterial blood flow was held constant by a pump and left atrial pressure was not permitted to change during nerve stimulation, the increase in lobar arterial pressure reflected an increase in vascular resistance across the lung (approximately 25% at 30 cps). The increase in resistance was across the entire lobe (from the tip of the perfusion catheter to the left atrium); therefore, the relative contribution of consecutive segments and of pre- and postcapillary vessels to the response could not be determined. The magnitude of the response of the pulmonary vascular bed to sympathetic nerve stimulation was related to the frequency of stimulation. The time from the onset of stimulation to attainment of the peak rise in pressure was inversely related to the frequency of stimulation, and the rise in pressure was well maintained during the period of stimulation. The response of the pulmonary vascular bed to nerve stimulation was antagonized by an alpha-blocking agent, indicating that this response is the result of activation of alpha receptors in the pulmonary vascular bed. The response of the lobe to injected norepinephrine was similar to its response to stellate stimulation in that dose-related increases in lobar arterial pressure occurred in the hemodynamically separated lobe.

Although the experiments presented in this study do not completely establish the mechanism of the response to sympathetic nerve stimulation, the data strongly suggest that active vasoconstriction resulting from the neurogenic release of norepinephrine in the lobar vessels occurred. The contribution of passive factors to the response to stellate stimulation was examined. Catheters were introduced using right heart techniques, and cannulation or dissection of the lung vessels was avoided. Blood flow to the lobe was held constant with a pump, and left atrial pressure was maintained constant, when necessary, by removing blood rapidly from that chamber through a transeptally placed withdrawal catheter. The volume, rate, and rhythm of respiration were maintained constant with a mechanical respirator, and the influence of bronchomotor activity was further excluded by observing the response to nerve stimulation after the respirator had been halted during expiration. Furthermore, airway resistance in the test lobe was not altered during nerve stimulation in three experiments during constant-volume respiration. The lack of change in airway pressure at constant-volume respiration during nerve stimulation is consistent with the observation that resting airways possess little dilator potential (15). These data suggest that changes in bronchomotor activity or in rate, rhythm, and volume of respiration did not contribute to the response of the pulmonary circulation to sympathetic stimulation.

The contribution of the bronchial circulation to the response to sympathetic nerve excitation was also evaluated in these experiments. Equalization of systemic arterial and lobar arterial pressures prevented significant transfer of blood from the bronchial circulation to the perfused lobar vascular bed. Since the response of the lobar bed to nerve stimulation during ventricular fibrillation was not significantly decreased, changes in bronchial circulation contributed little, if anything, to the response to stellate stimulation.

Earlier experiments (4–7), suggesting that sympathetic nerve stimulation increases vascular resistance in isolated perfused dog lungs, have been criticized because blood flow was low and nonpulsatile (8). The response to sympathetic stimulation might have been exaggerated by changes in blood viscosity at low shear rates. Furthermore, in other studies with canine lobes perfused in situ with a pulsatile pump, sympathetic nerve stimulation decreased the distensibility of the large pulmonary arteries and the precapillary bed but did not change the calculated pulmonary vascular resistance (8). Results of the present study corroborate the findings of Daly and co-workers that stimulation of the sympathetic nerves increases vascular resistance in the pulmonary vascular bed (4–7). Our results extend previous studies (4–7) by showing that sympathetic stimulation causes an increase in pulmonary vascular resistance over a wide range of stimulus frequency and that the responses can be elicited in a preparation in which the lobe is perfused at physiological flow rates with a pulsatile pump. The apparent discrepancy in the results of the present study and those of Ingram et al. (8) concerning the effect of stimulation on vascular resistance is not established by these data, although the results with alpha-blocking agents and norepinephrine are similar. However, manipulation, dissection, and external cannulation of lobar vessels in
any experimental procedure might damage the nerve supply to the vessels. Therefore, our study of the perfused dog lung indicates that stimulation of sympathetic nerves to the lung increases pulmonary vascular resistance approximately 25% at 30 cps. Since the contribution of passive factors (including changes in respiratory volume, rate, and rhythm, bronchomotor activity, and bronchial blood flow) was minimal, the response is attributed to active vasoconstriction mediated by activation of alpha receptors by neurally released norepinephrine in the pulmonary vascular bed.

References

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