Differential Effects of Phentolamine and Bretylium on Pulmonary Vascular Responses to Norepinephrine and Nerve Stimulation[1] (37550)

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Anatomical and histochemical studies indicate that in most species the pulmonary vascular bed is innervated by the sympathetic nervous system and it is well established that catecholamines are present in the walls of pulmonary blood vessels (1–4). However, the role of the sympathetic nervous system in regulating the pulmonary circulation is not well understood. Reports in the literature concerned with the influence of sympathetic nerve stimulation on the pulmonary circulation are controversial (5–11). In a recent study using a new right heart catheterization technique, we were able to show that electrical excitation of the stellate ganglia increases pulmonary vascular resistance and that passive factors, such as alterations in respiration, bronchomotor tone and the bronchial circulation, do not contribute to this response (12). The purpose of the present study was to compare pulmonary vasoconstrictor responses to sympathetic nerve stimulation and exogenous norepinephrine before and after administration of alpha receptor and sympathetic nerve terminal blocking agents.

Methods. Twenty-six mongrel dogs of either sex weighing 17 to 23 kg were anesthetized with pentobarbital sodium 30 mg/kg iv and were strapped to a fluoroscopic table. A 23 F balloon catheter was introduced from the left external jugular vein into the artery of the left lower lobe under fluoroscopic guidance. A 0.9 mm catheter 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 passed into the main pulmonary artery, the femoral artery, and into the left atrium transseptally. All pressures were measured with Statham P23D transducers and recorded on an oscilloscopic recorder (Electronics for Medicine, Inc., White Plains, NY). Mean pressures were obtained from the pulsatile signal by electrical averaging. Systemic injections were made through a catheter in the femoral vein. The techniques used in these experiments have been described previously (13).

After all catheters were positioned and the animals heparinized (300 units/kg), the balloon on the perfusion catheter was distended with 2–4 ml Hypaque until pressure in the perfused lobar artery decreased to near left atrial pressure. The left lower lobe was perfused with a Sarns pump with blood withdrawn from the right atrium. A standard lead II electrocardiogram was monitored on the oscilloscopic recorder. The animals were ventilated with a Harvard respirator through a cuffed endotracheal tube with room air.

The left stellate ganglia was approached through a left thoracotomy and the nerve was carefully isolated and placed upon a shielded Harvard electrode. The nerve was stimulated with square wave pulses of 2 msec duration, supramaximal voltage, for 30–45 sec periods with a Grass stimulator (Model S48 and SIU5 isolation unit) at 3, 10, and 30 Hz. The flow rate of the Sarns pump was adjusted so that perfusion pressure in the lobar artery approximated pressure in the main pulmonary artery, and thereafter the flow rate was not changed during the experiment. The flow rate averaged 350 ml/min in 26 experiments.

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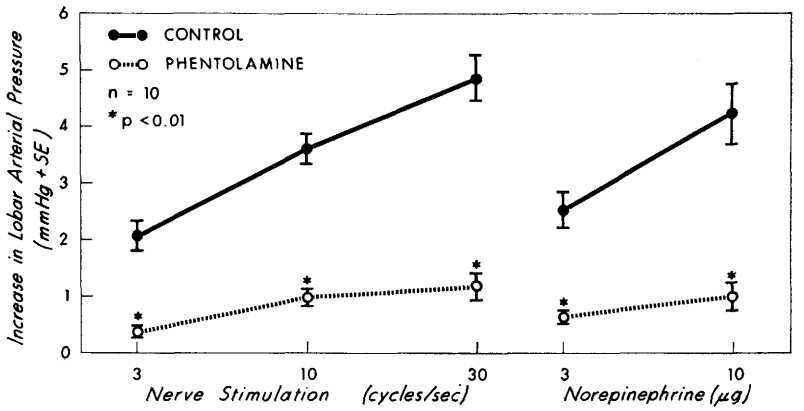

FIG. 1. Effect of phentolamine on pulmonary vasoconstrictor responses to sympathetic nerve stimulation and injected norepinephrine in the perfused dog lung preparation. Vasoconstrictor responses were obtained before and approximately 30 min after onset of infusion of phentolamine, 200–400 μg/min into the perfused lobar artery. *N* indicates number of dogs.

Norepinephrine injections (*l*-norepinephrine hydrochloride dose in terms of base) were made directly into the perfusion circuit in small volumes (3 and 10 μg in 0.03 and 0.10 ml). Phentolamine hydrochloride 200–400 μg/min, and bretylium tosylate 500 μg/min, were infused into the perfused lobar artery over a 30 to 60 min period with a Harvard infusion pump. Serotonin creatinine sulfate dose in terms of base was injected into the perfusion circuit as it entered the lobe. The hemodynamic data were evaluated using methods described by Snedecor for paired and group comparisons (14). A *p* value of less than 0.05 was considered significant.

Results. The effects of phentolamine and bretylium on pulmonary vascular responses to sympathetic nerve stimulation and injected norepinephrine were evaluated by comparing dose and stimulus–response curves in the presence and absence of the pharmacologic blocking agents in 2 groups of dogs. In both groups of animals electrical stimulation of the left stellate ganglia at 3, 10 and 30 Hz produced a significant stimulus-related increase in lobar arterial perfusion pressure (Figs. 1 and 2). Direct injection of norepinephrine, 3 and 10 μg, into the perfusion

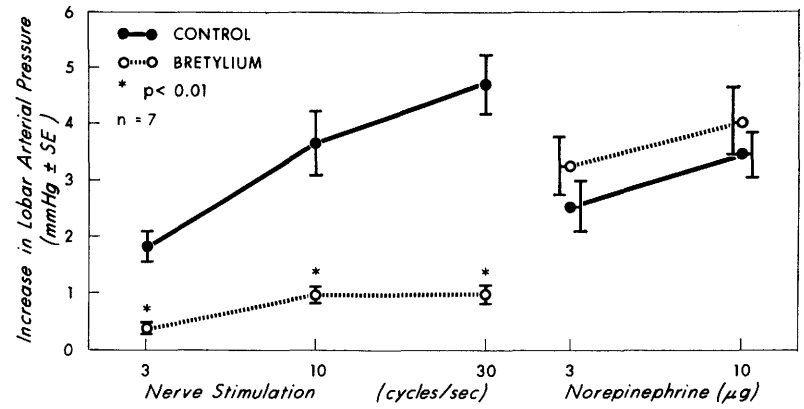

FIG. 2. Effect of bretylium on pulmonary vasoconstrictor responses to sympathetic nerve stimulation and injected norepinephrine in the perfused dog lung preparation. Vasoconstrictor responses were obtained before and approximately 30 to 45 min after onset of infusion of bretylium 500 μg/min into the lobar artery. *N* indicates number of dogs.

TABLE I. Effect of Phentolamine and Bretylium on Pressures in the Femoral Artery, Main Pulmonary Artery, Perfused Lobar Artery and Left Atrium.[a]

	Artery			
	Femoral	Main pulmonary	Perfused lobar	Left atrium
Control	88 ± 3	17 ± 1	21 ± 1	6 ± 1
Phentolamine $n = 10$	74 ± 4[b]	16 ± 1	20 ± 2	5 ± 1
Control	82 ± 6	16 ± 2	21 ± 1	4 ± 1
Bretylium $n = 7$	80 ± 8	14 ± 1	21 ± 1	4 ± 1

[a] mm Hg ± SE.
[b] Significantly different from control ($p < 0.05$).

circuit also produced a significant dose-related increase in lobar arterial perfusion pressure (Figs. 1 and 2). Since blood flow to the lobe was maintained constant by the pump and left atrial pressure either decreased or was unchanged, the increase in lobar arterial pressure with both nerve stimulation and norepinephrine reflects an increase in vascular resistance across the lung lobe.

Infusion of phentolamine 200–400 μg/min directly into the lobar artery produced only small changes in pressure in the perfused lobar artery, main pulmonary artery, and left atrium but caused a marked decrease in systemic arterial pressure (Table I). Pressor responses to both sympathetic stimulation and norepinephrine were decreased significantly at each dose of norepinephrine and each stimulus frequency during infusion of the alpha receptor blocking agent (Fig. 1). The specificity of the alpha adrenergic blockade was evaluated by comparing the effect of phentolamine on pulmonary vasoconstrictor responses to graded doses of norepinephrine and serotonin in 5 other dogs. Infusion of phentolamine, 200–400 μg/min, directly into the perfusion circuit produced similar changes in pressures in the femoral artery, main pulmonary and lobar arteries and left atrium as seen with this agent in the first group of dogs shown in Table I. In the presence of phentolamine responses to norepinephrine decreased markedly whereas responses to serotonin were not decreased significantly during constant infusion of the alpha blocking agent (Fig. 3).

Infusion of bretylium, 500 μg/min directly into the perfused lobar artery in 7 animals elicited little or no change in lobar arterial, pulmonary arterial, systemic arterial or left atrial pressure (Table I). Although bretylium was without significant effect on vascular pressures in the dog, it significantly decreased the response to sympathetic nerve stimulation at all stimulus frequencies studied (Fig. 2). Bretylium did not, however, modify the response to injected norepinephrine (Fig. 2). In order to determine the effect of time alone on pulmonary vascular responses to norepinephrine and nerve stimulation, responses

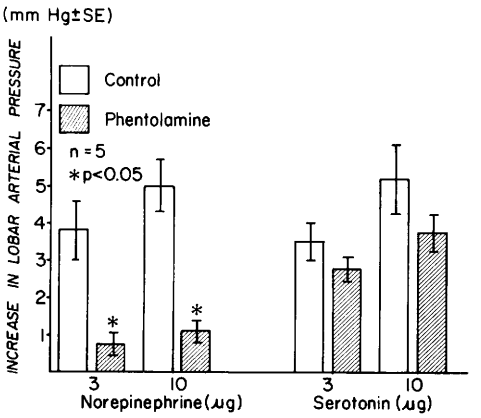

FIG. 3. Effect of phentolamine on pulmonary vasoconstrictor responses to norepinephrine and serotonin in the perfused dog lung preparation. Responses were obtained before and approximately 30 min after onset of infusion of phentolamine 200–400 μg/min into the lobar artery. *N* indicates number of dogs.

were obtained before and 30–45 min after onset of saline infusion, 0.1–0.2 ml/min, into the perfused lobar artery in 4 dogs. Responses to nerve stimulation and norepinephrine were not significantly different when saline rather than phentolamine or bretylium was infused over this period of time.

Discussion. Previously we reported that stimulation of the sympathetic nerves to the lung increased pulmonary vascular resistance under conditions of controlled blood flow using a new right heart catheterization technique. The response to nerve stimulation was independent of changes in respiration, bronchomotor tone and the bronchial circulation (12). It was therefore concluded that the increase in vascular resistance in response to nerve stimulation was due to active vasoconstriction in the pulmonary vascular bed. Results of the present study using specific pharmacologic blocking agents extend this observation by showing that responses to both exogenous and endogenous nerve released norepinephrine but not serotonin are antagonized by phentolamine, an alpha receptor blocking agent. In contrast, pulmonary vasoconstrictor responses to nerve stimulation but not norepinephrine were blocked by bretylium, an agent that decreases the amount of norepinephrine released per stimulus from sympathetic nerve terminals (15). These observations indicate that the active increase in pulmonary vascular resistance with nerve stimulation is the result of activation of alpha adrenergic receptors in the pulmonary vessels by endogenous norepinephrine released from sympathetic nerve endings.

The increase in pulmonary vascular resistance with nerve stimulation and norepinephrine (25% at 30 Hz and 10 μg) was across the entire lung lobe (lobar artery to the left atrium) so that the relative contribution of consecutive segments and of pre- and postcapillary vessels is unknown at the present time. There is, however, suggestive evidence that the pulmonary lobar veins may contribute to the increase in vascular resistance with nerve stimulation and norepinephrine (16). Preliminary observations indicate that during nerve stimulation and norepinephrine injection the pressure gradient from the small lobar vein and left atrium increases (16).

The present results confirm the findings of Daly and co-workers (5–8) that sympathetic stimulation increases pulmonary vascular resistance. Our results extend these early findings by showing (a) pulmonary vascular resistance is increased at stimulus frequencies which are in the physiologic range of discharge for sympathetic nerves and (b) specific adrenergic blocking agents antagonize the responses to neural stimulation indicating that an adrenergic mechanism is involved.

Present results concerning the effect of sympathetic stimulation on pulmonary vascular resistance are at variance with the studies of Ingram and co-workers (9–11). The reason for this apparent discrepancy in results is uncertain. However, it is possible that dissection and external cannulation of lobar vessels, procedures which are avoided using right heart techniques, may interfere with the innervation of the lobar vessels.

Summary. The effects of specific adrenergic blocking agents on pulmonary vascular responses to sympathetic nerve stimulation and norepinephrine were evaluated in the perfused dog lung using a new right heart catheterization procedure which avoids dissection and cannulation of lobar vessels. The increase in pulmonary vascular resistance in response to nerve stimulation and norepinephrine but not serotonin was antagonized by phentolamine, an alpha receptor blocking agent. Responses to nerve stimulation but not exogenous norepinephrine were antagonized by bretylium, an adrenergic nerve terminal blocking agent. It is concluded that the pressor response to nerve stimulation is due to activation of alpha receptors by endogenous norepinephrine released from sympathetic nerve endings in the pulmonary blood vessels.

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