PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 147, 68–71 (1974)

# Effect of Sympathetic Nerve Stimulation on Pulmonary Vascular Resistance in the Intact Spontaneously Breathing Dog[1] (38282)

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Anatomic, histochemical, and biochemical studies indicate that the pulmonary vascular bed is innervated by the sympathetic nervous system and that large quantities of norepinephrine are present in canine pulmonary arteries and veins (1–5). Although the supply of sympathetic nerves is abundant and considerable amounts of transmitter are found in pulmonary vessels, the role of the sympathetic nervous system in regulating the pulmonary vascular bed is uncertain. It has been reported by Daly and associates (6–9) that stimulation of the sympathetic nerves to the lung increases pulmonary vascular resistance under conditions of controlled blood flow. In contrast, other investigators found no increase in pulmonary vascular resistance in response to nerve stimulation in the perfused canine lung, but found instead that nerve stimulation decreased the distensibility of large pulmonary arteries (10–12). In a recent study using a new right heart catheterization technique which avoids procedures such as lung dissection and vessel cannulation which may interfere with the innervation of the lung, nerve stimulation was found to increase pulmonary vascular resistance (13). The increase in pulmonary vascular resistance was stimulus related over a wide range of stimulus rate and was similar when the lung was perfused with pulsatile and roller pumps (13). In addition, the response to nerve stimulation was independent of changes in respiration, bronchomotor tone, and bronchial circulation (13). In other studies it was shown that the effects of nerve stimulation and injected norepinephrine are similar and that the increase in pulmonary vascular resistance with both nerve released and exogenous transmitter could be blocked by an alpha receptor blocking agent (14). However, all previous studies were carried out in the open chest dog with positive pressure ventilation or with the respirator stopped temporarily in expiration. The purpose of the present study was to evaluate the effects of sympathetic nerve stimulation on the pulmonary circulation in the intact spontaneously breathing dog.

*Methods.* Five beagles and one greyhound weighing 14–17 kg, all of whom were free of heart worms and in good health, were used in the present study. The animals were anesthetized with pentobarbital sodium 30 mg/kg iv and were strapped in the supine position to a fluoroscopic table. A 20F balloon catheter was introduced from the left external jugular vein and positioned in the artery of the left lower lung lobe under fluoroscopic guidance. A 0.9-mm catheter with its tip positioned about 2 cm past the tip of the balloon catheter was used to measure pressure in the perfused lobar artery. Catheters with side holes were passed into the main pulmonary artery, the aorta, and into the left atrium transseptally. All vascular pressures were measured with Statham P23D transducers zeroed at midchest level and were recorded on an oscilloscopic recorder, model DR- 12 (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 in detail previously (15, 16).

After all catheters were positioned and the animals heparinized (300 U/kg), the balloon on the perfusion catheter was distended with 2–4 ml

[1] Supported by U. S. Public Health Service Grants HL 11802 and 15580 and a grant from the American Heart Association.

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Hypaque until pressure in the perfused lobar artery decreased to near left atrial pressure. The left lower lung lobe was then pump perfused (Sarns roller pump) with blood withdrawn from the right atrium. The flow rate of the 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 325 ml/min in the six experiments. A standard lead II electrocardiogram was monitored on the oscilloscopic recorder.

In three of the beagles, the left stellate ganglion was approached through the second interspace under pentobarbital anesthesia and a Medtronics Angiostat was placed around the nerve and the chest was closed. The angiostat leads were tunneled under the skin to the back of the neck where they were brought out at the time of the experiment. The animals were given $10^6$ U penicillin and returned to the vivarium. After 10–21 days, the animals with the chronically implanted electrodes were catheterized. In the other three dogs, the Angiostat was placed around the stellate ganglion the the chest was carefully closed and aspirated and the animals were permitted to breathe spontaneously. In both acute and chronic experiments, the stellate ganglia were stimulated with square wave pulses, 2-msec duration, supramaximal voltage, for 30–45-sec periods with a Grass stimulator (Model S 48). The stimulus was isolated from the ground with a Grass SIU5 isolation unit. The nerve was stimulated at 3, 10, and 30 Hz and the stimulus frequency was randomized.

Norepinephrine (l-norepinephrine hydrochloride dose in terms of base) was injected into the perfusion circuit in small volumes (3 and 10 $\mu$g in 0.03 and 0.10 ml). Phentolamine hydrochloride 200 $\mu$g/min was infused into the perfused lobar artery for a period of 10–30 min with a Harvard infusion pump. The hemodynamic data were evaluated using the method of Snedecor for paired comparison (17). A $P$ value of less than 0.05 was considered significant.

*Results.* The effects of nerve stimulation and injected norepinephrine on the pulmonary circulation in six intact spontaneously breathing dogs are summarized in Table I and Fig. 1. Direct electrical stimulation of the sympathetic nerves to the lung in the range of frequency of 3–30 Hz increased lobar arterial pressure in a stimulus-related manner. Injection of norepinephrine 3 and 10 $\mu$g into the perfusion circuit also increased lobar arterial pressure in a dose-related manner. Since blood flow to the lung lobe was

TABLE I. Effect of Sympathetic Nerve Stimulation and Norepinephrine on Pressures in the Lobar Artery Left Atrium, Main Pulmonary Artery, and Aorta.

| | Pressure (mm Hg ± SEM) | | | |
|---|---|---|---|---|
| | Lobar Artery | Left atrium | Main pulmonary artery | Aorta |
| Sympathetic nerve stimulation ($N$ = 6) | | | | |
| Control | 18.7 ± 2.0 | 2.0 ± 1.6 | 14.4 ± 0.8 | 93.0 ± 10.9 |
| 3 Hz | 20.2 ± 1.9* | 1.0 ± 1.5* | 16.4 ± 1.1* | 101.0 ± 11.1 |
| Control | 20.0 ± 1.2 | 2.3 ± 1.4 | 14.0 ± 0.6 | 84.2 ± 8.4 |
| 10 Hz | 22.8 ± 1.4* | 1.4 ± 1.5* | 16.2 ± 1.3* | 100.8 ± 9.5* |
| Control | 19.9 ± 1.0 | 2.3 ± 1.4 | 14.2 ± 1.1 | 86.7 ± 8.7 |
| 30 Hz | 23.9 ± 1.1* | 1.5 ± 1.6 | 15.7 ± 2.5 | 105.8 ± 10.0* |
| Norepinephrine ($N$ = 6) | | | | |
| Control | 18.3 ± 1.1 | 2.0 ± 1.3 | 13.3 ± 0.8 | 83.3 ± 8.3 |
| 3 $\mu$g | 21.5 ± 1.3* | 2.0 ± 1.5 | 14.8 ± 2.2 | 109.2 ± 15.2* |
| Control | 18.7 ± 1.4 | 2.2 ± 1.4 | 13.2 ± 0.8 | 81.7 ± 7.5 |
| 10 $\mu$g | 22.8 ± 1.7* | 1.8 ± 1.7 | 16.8 ± 1.4* | 117.5 ± 15.5* |

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

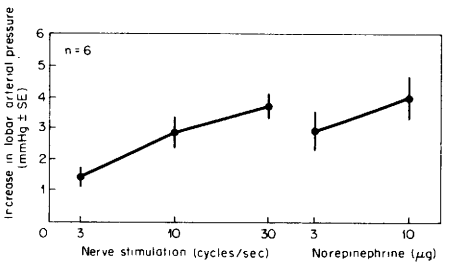


FIG. 1. Effect of direct electrical stimulation of the left stellate ganglion and injected norepinephrine on lobar arterial pressure in six intact spontaneously breathing dogs. The increase in lobar arterial pressure was significant at each stimulus frequency and dose of norepinephrine ($P < 0.05$).

maintained constant by the pump and left atrial pressure was either decreased or unchanged, the increase in the pressure gradient from lobar artery to left atrium reflects an increase in vascular resistance across the left lower lung lobe. Stimulation of the sympathetic nerves to the lung at 3 and 10 Hz and the 10-$\mu$g dose of norepinephrine increased pressure in the main pulmonary artery significantly. Nerve stimulation at 10 and 30 Hz and injection of both doses of norepinephrine increased pressure significantly in the aorta.

In 3 of the 6 spontaneously breathing dogs, the effects of phentolamine, an alpha receptor blocking agent, on responses to nerve stimulation and norepinephrine were evaluated. In these experiments, control responses to norepinephrine and nerve stimulation were obtained and phentolamine was infused into the perfusion circuit at a rate of 200 $\mu$g/min. During infusion of phentolamine, the increase in lobar arterial pressure in response to nerve stimulation and injected norepinephrine was decreased significantly, at each stimulus frequency and dose of the sympathomimetic amine studied (Fig. 2). Infusion of phentolamine decreased pressure in the aorta by about 20 mm Hg but had little or no effect on pressures in the lobar artery, left atrium, or main pulmonary artery.

*Discussion.* In a previous report, electrical stimulation of the sympathetic nerves to the lung was shown to increase pulmonary vascular resistance in the dog under conditions of controlled blood flow (13). The response to nerve stimulation was independent of changes in respiration, bronchomotor tone, and the bronchial circulation, and injected norepinephrine had similar effects on the pulmonary circulation (13). In other studies, the increase in pulmonary vascular resistance in response to norepinephrine and nerve stimulation was inhibited by an alpha receptor blocking agent (14). In addition, the response to nerve stimulation but not norepinephrine was antagonized by bretylium, an adrenergic nerve terminal blocking agent (14). It was therefore concluded that the increase in pulmonary vascular resistance with nerve stimulation was the result of active vasoconstriction in the pulmonary vascular bed and that this vasoconstriction is due to activation of alpha receptors by norepinephrine released from nerve terminals in the pulmonary vessels. Results of preliminary studies in our laboratory indicate that the increase in pulmonary vascular resistance is probably mediated by vasoconstriction in both lobar veins and vessels upstream in the precapillary bed.

However, all previous studies concerned with the effects of nerve stimulation on the pulmonary circulation under conditions of controlled blood flow were carried out in open-chest animals (6–11, 13, 14). In the present study, the effects of direct electrical stimulation of the sympathetic nerves to the lung on pulmonary vascular resistance were evaluated in the intact spontaneously breathing dog. Results of these experiments show that stimulation of the sympathetic nerves results in a significant stimulus-related increase in lobar arterial pressure in the intact animal. Since blood flow to the lung was held constant by the pump and left atrial pressure was either decreased or unchanged, the increase in lobar arterial pressure reflects an increase in vascular

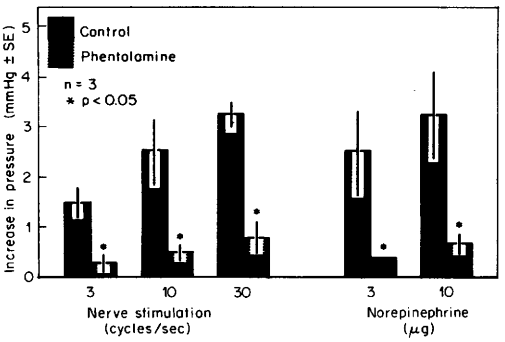


FIG. 2. Effect of phentolamine on the increase in lobar arterial pressure in response to stellate ganglion stimulation and norepinephrine injection in three intact spontaneously breathing dogs. Responses to nerve stimulation and injected norepinephrine were determined before and 10–30 min after onset of the phentolamine infusion.

resistance across the left lower lung lobe. Furthermore, the increase in vascular resistance with both nerve stimulation and injected norepinephrine was blocked by phentolamine, and alpha receptor blocking agent. These results indicate that in the intact spontaneously breathing dog, the pressor response to sympathetic nerve stimulation is mediated by alpha adrenergic receptors. Results of the present studies in the intact spontaneously breathing dog are consistent with previous studies in the open chest animal in which nerve stimulation was shown to increase pulmonary vascular resistance in a similar stimulus related fashion (13, 14).

*Summary*. The effects of sympathetic nerve stimulation on pulmonary vascular resistance under conditions of controlled blood flow were evaluated in the intact spontaneously breathing dog. Stimulation of the sympathetic nerves to the lung resulted in a significant stimulus-related increase in pulmonary vascular resistance in the intact animal. Injected norepinephrine had similar effects on the pulmonary vascular bed and responses to both norepinephrine and nerve stimulation were blocked by phentolamine, an alpha receptor blocking agent. It is concluded that the pressor response to nerve stimulation is mediated by alpha receptors in the pulmonary vascular bed and that this response is similar in magnitude in both the intact spontaneously breathing and open-chest animal.

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Received April 29, 1974. P.S.E.B.M., 1974, Vol. 147.