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Sympathetic Nerve Stimulation and Vascular Resistance in a Pump-Perfused Dog Lung Lobe[1] (40383)

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In spite of the currently renewed interest in the role of neural control over pulmonary hemodynamics (3, 6, 7), the influence of sympathetic nerve stimulation on pulmonary hemodynamics is not entirely clear at the present time. Daly *et al.* (1), Kadowitz and Hyman (2) and Kadowitz *et al.* (3) have observed increases in pulmonary vascular resistance in response to sympathetic nerve stimulation, while Ingram *et al.* (4) and Aarseth *et al.* (5) observed changes in vascular compliance and blood volume which were not associated with changes in vascular resistance. The reasons for these differences are not clear. However, questions regarding differences in the experimental preparations used have been raised (2). The present study was carried out to characterize the hemodynamic responses of a pump-perfused *in situ* left lower lobe (LLL) of the dog lung to stellate ganglion stimulation. This was done to determine whether this preparation could be utilized to study neural and reflex control of the pulmonary circulation.

Materials and methods. Thirteen mongrel dogs (19.3 ± 1.8 SD kg) were used. Ten of these dogs were anesthetized with sodium pentobarbital (30 mg/kg iv) and three with sodium pentothal (15 mg/kg iv) followed by chloralose (40 mg/kg iv). After placement of femoral artery and vein catheters and a Carlens double lumen tracheal tube, the dogs were paralyzed with succinyl choline (2 mg/kg iv). Supplemental doses of the drugs were administered during the course of the experiments.

A left thoracotomy was performed. The left upper lobe artery vein and bronchus were tied off and the lobe was removed. After the dog was heparinized (1350 units/kg), approximately 200 ml of blood were removed via the femoral artery catheter and used to prime the extracorporeal perfusion system. During this bleeding procedure, 200 ml of 6% Gentran 75 were infused into the dog to replace this volume, and no changes in arterial blood pressure were observed. Cannulas were placed in the left pulmonary artery just proximal to the left upper lobe artery and in the LLL vein via the left atrial appendage and secured with a tie around the vein. The perfusion system was a closed system in which the blood was pumped (Masterflex 7545) into the left pulmonary artery and allowed to drain into a reservoir, from which it was pumped back into the lobar artery. The flow rate was constant throughout the entire perfusion period for each of the LLL preparations studied. The mean value for the 13 LLL preparations was 319 ± 62 SD ml/min. Pressures were measured from side ports in the arterial and venous cannulas relative to the top of the LLL. The venous outflow pressure was set at 2.4 ± 0.8 SD torr by adjusting the height of the reservoir. The perfusion system included a heat exchanger to maintain the temperature of the blood at 37°, and the dog was placed on a heating blanket to help maintain constant body temperature.

The right lung and LLL were ventilated separately using a double piston respirator. Airway pressures were measured from pressure taps in the tubes leading to the right lung and LLL, and end-expiratory pressures were maintained at approximately 2 torr. The right lung was ventilated with a gas mixture containing 30% O_2 in N_2. Tidal volume and frequency were adjusted to maintain the arterial PCO_2 near 40 mm Hg, and $NaHCO_3$ was infused as necessary to maintain arterial pH near 7.4. The LLL was ventilated with a

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mixture containing approximately 6% CO_2 and 15% O_2 in N_2. Femoral artery blood gases were: PO_2, 127 ± 24 SD torr; PCO_2, 37 ± 5 SD torr; pH, 7.35 ± 0.04 SD. Blood in the LLL perfusion system had a PO_2 of 100 ± 6 SD torr, PCO_2 of 37 ± 4 SD torr, and pH of 7.38 ± 0.03 SD. Hypoxic vasoconstriction was induced by ventilating the LLL with a gas mixture containing approximately 6% CO_2 and 3% O_2 in N_2. This reduced the PO_2 in the LLL perfusion system to 29 ± 4 SD torr.

The left stellate ganglion was isolated and electrical stimulation of the ganglion was accomplished using a Grass SD-9 stimulator and Harvard shielded electrodes. Stimulus response curves were obtained on six of the lobe preparations by increasing the stimulus frequency over the range of 0–20 Hz using 3-, 5-, 10- or 20-volt stimuli. In all cases, the stimulus duration was 2 msec.

In seven lobe preparations, the change in lobar artery pressure in response to stellate ganglion stimulation (stimulus parameters: 15 Hz, 20 volts, 2 msec duration), injection of norepinephrine (5 μg) into the lobar artery, and hypoxic vasoconstriction was observed before and after adding 5 mg of phentolamine mesylate to the isolated perfusion system.

In six of the lobes, the influence of stellate ganglion stimulation on left lobar blood volume was determined from the mean transit time for indocyanine green dye. Fifty micrograms of dye were injected into the inflow tubing just proximal to a mixing chamber. The outflow blood was continuously sampled using a Harvard withdrawal pump to draw blood through a Gilson cuvette densitometer, from a mixing chamber in the outflow tubing. The mean transit time for the dye through the perfusion system, with the LLL excluded, was subtracted from that including the lobe in order to obtain the lobe mean transit time during control conditions and during stellate ganglion stimulation (stimulation parameters: 15 Hz, 20 volts, 2 msec duration). During the blood volume measurements, ventilation of the lobe was halted at end expiration.

Results. The stimulus response curves showing the influence of the strength and frequency of stellate ganglion stimulation on the lobar artery pressure are shown in Fig. 1. Since flow and outflow pressures were constant, the increases in pressure reflect increases in lobar vascular resistance in response to sympathetic nerve stimulation. The maximum response appears to have been elicited above 10 volts and 15 Hz. Since the type of anesthetic used did not appear to influence the magnitude of the response, the stimulus response curves include the three chloralose anesthetized dogs and three pentobarbital anesthetized animals.

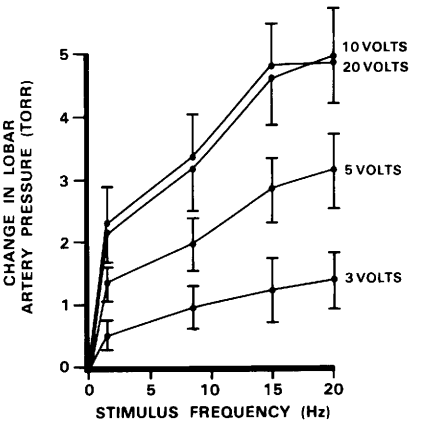

FIG. 1. Influence of stellate ganglion stimulus voltage and frequency on the increase in lobar artery pressure (± SE); stimulus duration, 2 msec. Mean control lobar artery pressure was 11.8 ± 0.5 SE torr (n = 6).

Figure 2 is a tracing of the systemic arterial pressure and the lobar arterial pressure in response to stellate ganglion stimulation before and after the addition of phentolamine to the isolated lobar perfusion system. The phentolamine had no effect on the baseline LLL perfusion pressure or on the systemic response to stellate ganglion stimulation, but it abolished the response in the LLL. Figure 3 shows the LLL response to stellate ganglion stimulation, norepinephrine infusion and hypoxia before and after the addition of phentolamine to the lobar perfusion system. Phentolamine blocked the responses to nerve stimulation and norepinephrine infusion. In fact, after phentolamine a small but consistent decrease in pressure occurred in response to these stimuli. Phentolamine had no influence on the magnitude of the hypoxic vasoconstrictor response in this preparation.

Table I shows the influence of stellate ganglion stimulation on lobar artery pressure and blood volume at two lobar venous pressures. Stellate ganglion stimulation had no influ-

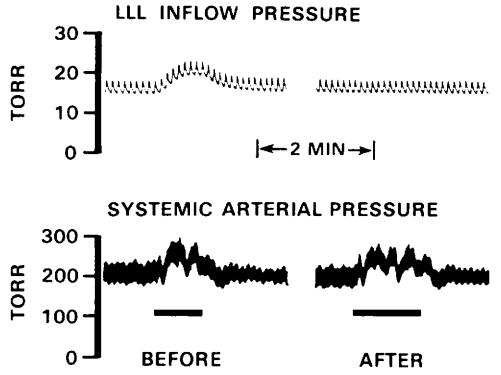

FIG. 2. Left lower lobar artery pressure and systemic arterial pressure tracing showing the influence of stellate ganglion stimulation before and after phentolamine was added to the isolated perfusion system. Bars represent period of electrical stimulation of the stellate ganglion.

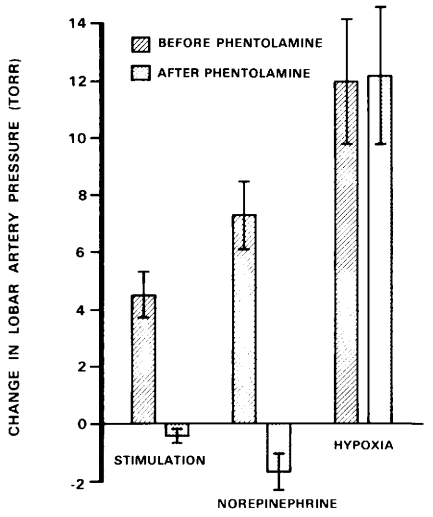

FIG. 3. Influence of stellate ganglion stimulation, norepinephrine infusion and hypoxia on lobar artery pressure (± SE) before and after the addition of phentolamine to the isolated perfusion system. Mean control lobar artery pressure was 14.0 ± 1.3 SE torr (n = 7).

ence on blood volume at the low outflow pressure and, although there was a tendency for the blood volume to be smaller during stimulation at the higher outflow pressure, the change was not statistically significant ($0.06 > P > 0.05$). The increase in blood volume, when the outflow pressure was raised from 2 to 15 torr, was smaller ($P < 0.05$) during stellate ganglion stimulation, which may indicate a decrease in vascular compliance.

Discussion. The results of this study support the concept that sympathetic nerve stimulation can increase pulmonary vascular resistance. In this respect, the results are similar to those obtained by Kadowitz and Hyman (2), Kadowitz *et al.* (3) and Daly *et al.* (1) but unlike those of Ingram *et al.* (4) and Aarseth *et al.* (5). While the reasons for these differences in response to sympathetic stimulation are not clear, the present study indicates that the *in situ* perfused LLL of the dog lung provides a useful tool for studying the influence of sympathetic stimulation on pulmonary hemodynamics. Since the magnitude of the increase in resistance was similar to that previously reported by Kadowitz and Hyman (2) and Kadowitz *et al.* (3), it would appear that direct cannulation of the left pulmonary artery which requires dissection of the artery as opposed to catheterization of the artery via the right heart (2) is not a major factor determining the response to stellate ganglion stimulation.

The response was blocked by the α-adrenergic blocking agent, phentolamine, which also blocked the response to norepinephrine. This was apparently a specific inhibition, since the hypoxic vasoconstriction was not influenced by the α-adrenergic blockade. This lack of influence of α-adrenergic blockade on hypoxic vasoconstriction has been

TABLE I. INFLUENCE OF SYMPATHETIC NERVE STIMULATION ON LEFT LOBAR ARTERY PRESSURE AND BLOOD VOLUME.[a]

Condition	Outflow pressure (torr)	Lobar artery pressure (torr)	$P<$	Blood volume (ml)	$P<$
Control	2	16.0 ± 1.6	0.002	22.3 ± 2.4	NS
SGS	2	20.5 ± 2.2		22.9 ± 2.6	
Control	15	24.9 ± 1.4	0.003	32.4 ± 3.3	NS
SGS	15	27.2 ± 1.5		30.4 ± 2.9	

[a] SGS = stellate ganglion stimulation. Values shown are mean ± SE; n = 6. P values are for paired t test on differences between control and nerve stimulation. NS = difference is not statistically significant.

observed previously in calves by Silove and Grover (8). However, pulmonary hypoxic constriction has been attenuated by α-adrenergic receptor blockade in the cat (9).

The influence of stellate ganglion stimulation on lobar blood volume was less pronounced than on vascular resistance. While the results are compatible with some decrease in vascular compliance, they do not appear to indicate large changes in the overall distensibility of the lobar vasculature. Local changes such as a decrease in lobar arterial distensibility observed by Ingram *et al.* (4) would not necessarily be detected by measurements of total volume changes. In this study, there was a tendency for the blood volume to be reduced by sympathetic stimulation at the high venous pressure, as previously reported by Aarseth *et al.* (5). However, the effect was small and may have been modified by the increase in vascular pressure, which was not observed by Aarseth *et al.* (5).

Summary. The pump-perfused *in situ* left lower lobe of the dog lung responded to electrical stimulation of the stellate ganglion by increasing vascular resistance. A dose of phentolamine, which blocked the vasoconstrictor response to infused norepinephrine but not hypoxia, blocked the response to stellate ganglion stimulation. Sympathetic stimulation had relatively little influence on lobar blood volume, but appeared to decrease total lobar vascular compliance.

1. Daly, I. de B., Ramsey, D. J., and Waaler, B. A., J. Physiol. (London) **209,** 317 (1970).
2. Kadowitz, P. J., and Hyman, A. L., Circ. Res. **32,** 221 (1973).
3. Kadowitz, P. J., Knight, D. S., Hibbs, R. G., Ellison, J. P., Joiner, P. D., Brody, M. J., and Hyman, A. L., Circ. Res. **39,** 191 (1976).
4. Ingram, R. H., Szidon, J. P., Skalak, R., and Fishman, A. P., Circ. Res. **22,** 801 (1968).
5. Aarseth, P., Nicolaysen, G., and Waaler, B. A., Acta Physiol. Scand. **81,** 408 (1971).
6. Malik, A. B., J. Appl. Physiol. **42,** 335 (1977).
7. Kessler, J. R., and Cassin, S., Amer. J. Physiol. **1,** H671 (1977).
8. Silove, E. D., and Grover, R. F., J. Clin. Invest. **47,** 274 (1968).
9. Porcelli, R. J., and Bergofsky, E. H., J. Appl. Physiol. **34,** 483 (1973).

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