PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 164, 63–68 (1980)

Effect of Sympathetic Nerve Stimulation on Hypocapnic Airway Constriction (40825)[1]

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Alveolar hypocapnia, through a direct effect, produces constriction of peripheral airway smooth muscle (1–5). Vagally mediated airway constriction produced by increasing systemic arterial P_{CO_2} does not appear to affect the airway constrictor effects of low alveolar P_{CO_2} (4, 6). Vagal nerve stimulation superimposed on hypocapnic airway constriction produced results concordant with the previous studies which indicated different anatomical locations of the constrictor effects of these two stimuli (2). Little information is available regarding the effect of sympathetic nerve stimulation on hypocapnic airway constriction. Nisell (3) reported from only one experiment that stellate ganglion stimulation was ineffective in reducing hypocapnic airway constriction produced by decreasing the inspired CO_2 in the isolated cat lung pretreated with a constrictor agent. The purpose of this study was to investigate the effects of sympathetic nerve stimulation on hypocapnic airway constriction in the isolated left lower lobe of the canine lung.

Materials and methods. Two series of experiments were conducted to determine the effect of sympathetic nerve stimulation on hypocapnic airway constriction in the left lower lobe (LLL) of the canine lung. The methods used to isolate the LLL and to measure changes in pulmonary mechanics of the LLL are described in detail elsewhere (2, 7), and only the essence of these methods is presented here.

In the first series of experiments, the effects of sympathetic stimulation on hypocapnic airway constriction produced by acute lobar artery occlusion were studied. Mongrel dogs (15 to 30 kg) were anesthetized with sodium pentobarbital (30 mg/kg plus supplemental amounts as required) intubated and ventilated with a timer-operated solenoid ventilator. The left middle and upper lobes were removed through a left thoracotomy. A LLL tracheal cannula, tied in place by a suture around the main left bronchus, was used to ventilate the LLL separately from the remaining lobes of the lung. The LLL and the right lung of the animal were ventilated simultaneously with slow flow-rate inflations. During the expiratory period of the right lung, the LLL was ventilated with a high flow-rate, square flow pulse of short duration. Lobar pulmonary resistance and lung compliance were measured from this pulse. Pulmonary resistance was measured from the sudden drop in LLL airway pressure when flow was interrupted and expiration delayed 1 sec by the formula $R = \Delta P/F$. Dynamic compliance was measured from the peak pressure minus the ΔP resistance and static compliance from the pressure measured after expiration had been delayed 1 sec. Dynamic and static compliance were calculated from the ventilation volumes divided by the respective pressure measurements. Although referred to as static compliance measurements these are in fact quasistatic measurements (8). LLL airway pressure was recorded from a catheter placed in the LLL bronchus. The animal was ventilated with a volume and rate required to maintain normal blood gas and pH.

The left stellate ganglion was exposed and placed on bipolar stimulating electrodes. The left cervical vagus nerve was exposed and divided. The distal end was placed across bipolar electrodes. The stellate ganglion and cervical vagus stimulation parameters were usually 3 msec duration at 30 Hz with a current strength of 3 to 10 ma. Current strength for vagal nerve stimulation was selected to produce a definite cardiac slowing and stellate ganglion stimulation to

[1] This study was supported in part by the Medical Research Service of the Veterans Administration and by a grant from the American Lung Association.

0037-9727/80/050063-06$01.00/0

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produce a significant systemic arterial pressure response. Vagal stimulations were done to establish an airway constriction against which to test the effectiveness of the sympathetic nerve stimulations and thus stimulation parameters were not determined to be supramaximum. To assure that the sympathetic innervation to the lobe was intact, only preparations in which sympathetic nerve stimulation produced a reduction in the constrictor response produced by vagal stimulation were used. Hypocapnic airway constriction consequent to acute lobar artery occlusion was produced by tightening a snare ligature placed around the main left pulmonary artery. Stellate ganglion stimulation was initiated when lobar airway pressure began to increase as end-expired CO_2 decreased toward O% and was interrupted when the airway pressure response reached a maximum. Control values for hypocapnic constriction were either determined by acute lobar artery occlusion in the absence of stellate ganglion stimulation or from the peak pressure attained after the sympathetic stimulation had been terminated while the lobar artery remained occluded (3 of 11 runs). Changes in pulmonary mechanics are presented as percentage change from control and statistical analyses were made using a nonpaired *t* test.

The results of the first series of experiments could have been affected by the lack of blood flow during acute occlusion of the lobar artery. In the second series of experiments hypocapnic airway constriction and sympathetic stimulations were conducted during constant flow perfusion of the LLL. For this series the left pulmonary artery and LLL vein were cannulated. Blood perfused into the lobar artery passed through the LLL, drained into a temperature-controlled reservoir, and was recirculated through the LLL. Lobar perfusion pressure was measured from a T in the perfusion cannula.

Hypocapnic airway constriction was produced by reducing inspired CO_2 from 5 to 0% while lobar blood flow remained constant. Stellate ganglion stimulations were initiated as lobar airway pressure began to increase and terminated when a maximum response was attained. Controls were conducted in the absence of stellate ganglion stimulation. Changes in peak airway pressure of the fast flow trace were used as an index of changes in pulmonary mechanics. During stellate ganglion stimulation, the measurements of both lobar airway pressure and lobar perfusion pressure were made at the peak of the lobar artery response. The constrictor effect of sympathetic stimulation on the pulmonary vasculature (9) was used to assure that the lobar innervation had not been damaged by isolation of the LLL.

The stellate ganglion was also stimulated in some experiments after hypocapnic airway constriction had been produced. After stellate ganglion stimulation was terminated, the inspired CO_2 was increased to 5%. The effect of stellate ganglion stimulation versus the dilator effect of CO_2 on hypocapnic airway constriction was then compared.

Results. Ten animals were used for these studies. Figure 1 shows a record from an experiment in which (A) the left vagus nerve was stimulated, then (B) the left vagus nerve was stimulated in the presence of stellate ganglion stimulation, and (C) and left vagus nerve was again stimulated. Hypocapnic airway constriction was then produced in the absence (D), and presence (E) of stellate ganglion stimulation. The effectiveness of sympathetic nerve stimulation in blocking vagally induced bronchoconstriction was then tested again (F, G, and H). Systemic arterial blood pressure dropped with vagal stimulation, and a bradycardia was evident. The systemic blood pressure response produced by vagal stimulation in the presence of sympathetic nerve stimulation showed a slightly reduced response. However, a definite block of the vagally produced bronchoconstriction was present. Sympathetic nerve stimulation during hypocapnic airway constriction by contrast, appeared to have little effect on hypocapnic airway constriction.

An analysis of the results from the four animals used for this series is shown on the graph in Fig. 2. Sympathetic nerve stimula-

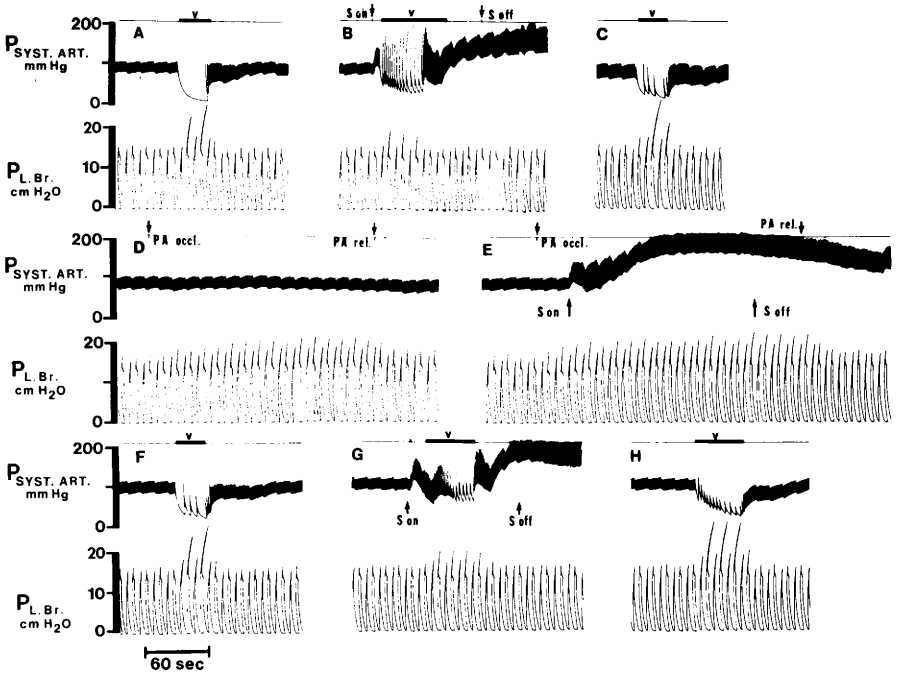

FIG. 1. Effect of sympathetic stimulation on the constrictor effects of vagal nerve stimulation versus its effect on hypocapnic airway constriction produced by lobar pulmonary artery occlusion. $P_{SYST.ART.}$, systemic arterial pressure; $P_{L.Br.}$, pressure from lobar bronchus; V, vagal nerve stimulation; $PA_{OCCL.}$ and $PA_{REL.}$, lobar pulmonary artery occluded and released; L_{ON} and S_{OFF}, sympathetic nerve stimulator on and off.

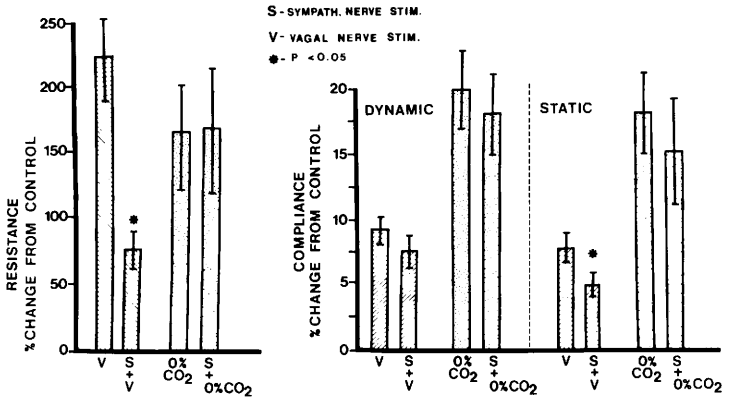

FIG. 2. Graphic comparison of the effect of sympathetic stimulation on vagally produced airway constriction, versus its effect on hypocapnic airway constriction (V—vagal stimulation, n = 32; S + V—sympathetic and vagal stimulation, n = 19; 0% CO_2—end-expired CO_2 to approximately 0% secondary to lobar artery occlusion, n = 11; S + 0% CO_2—sympathetic stimulation and end-expired reduced toward 0%, n = 11). Percentage increase in resistance and decrease in compliance graphed in absolute numbers.

tion significantly reduced the increase in resistance and decrease in static compliance produced by vagal stimulation. The decrease in dynamic compliance was also reduced, but not significantly. However, even though hypocapnic airway constriction produced a greater effect on compliance than did vagal stimulation, sympathetic nerve stimulation did not have a significant blocking effect on either the change in resistance or compliance.

Figure 3 shows a record from an experiment in which hypocapnic airway constriction was produced in the absence (A), presence (B), and absence (C) of stellate ganglion stimulation. With sympathetic stimulation there was an increase in lobar pulmonary artery pressure, but little, if any, effect on the hypocapnic airway constriction. The hypocapnic airway constriction was produced by decreasing the inspired CO_2 in the pump perfused preparation from 5 to 0%. Sympathetic stimulation was initiated as the inspired percentage CO_2 began to drop and lobar airway pressure to increase. Lobar airway pressure returned toward control when the inspired CO_2 was returned to 5%. Lobar airway pressure increased 32.2 ± 6.8% (n = 10) in six animals in the absence of sympathetic nerve stimulation and 35.3 ± 7.35% (n = 8) in the presence of sympathetic nerve stimulation. Sympathetic nerve stimulation produced an increase in lobar perfusion pressure of 20.5 ± 4.0% (n = 8). Returning the inspired CO_2 concentration back to 5% produced a significant decrease in peak airway pressure of −15.8 ± 2.1% (n = 16).

Sympathetic stimulation during existing hypocapnic airway constriction did not produce a significant reduction in LLL airway pressure. Analysis of the data from five experiments in three animals (n = 4–5) showed that airway pressure increased 45 ± 9.9% when inspired CO_2 was reduced from 5 to 0%. Sympathetic nerve stimulation produced a significant (33 ± 8.0%) increase in lobar artery perfusion pressure and a nonsignificant (−1.2 ± 1.2%) decrease in airway pressure. Increasing the inspired CO_2 back to 5% produced a −17.4 ± 2.2% decrease in airway pressure. Thus, in no experiment did sympathetic stimulation have an effect on hypocapnic airway constriction.

Discussion. Severinghaus *et al.* (5) suggested that the dilator effect of CO_2 on airways constricted by temporary unilateral pulmonary artery occlusion is a result of direct diffusion of gases into the smooth muscle of airways which are perfused by the pulmonary artery. According to McLaughlin *et al.* (10), this would be the smooth muscle of the respiratory bronchioles and alveolar ducts. Mann (11) in a study of seven mammals, not including the dog, however, did not find evidence for catecholamine-containing fibers in the respiratory bronchioles. Thus, anatomically, it is not surprising that sympathetic nerve stimulation did not have a direct effect on hypocapnic airway constriction. Further-

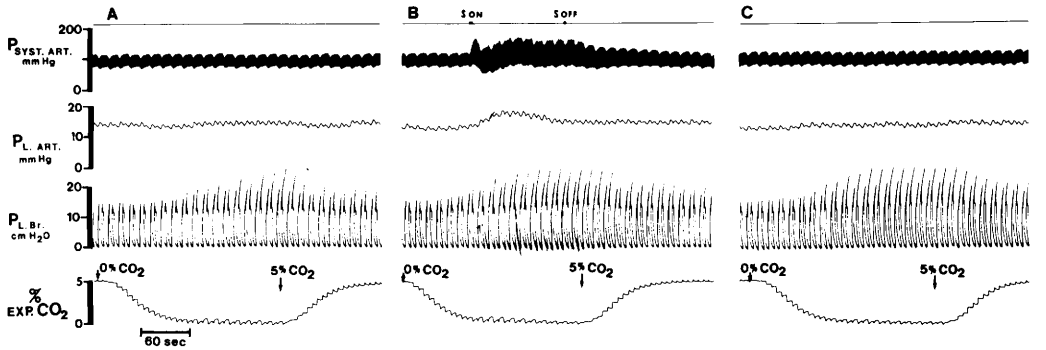

FIG. 3. Sympathetic nerve stimulation in an attempt to block hypocapnic airway constriction produced by reducing inspired CO_2 from 5 to 0%.

more, these results suggest that, even if sympathetic stimulation released sufficient mediator to partially block the constrictor effects of vagal nerve stimulation and to increase lobar artery pressure, insufficient mediator was released into the perfusate of the perfused preparation to have a significant effect on hypocapnic airway constriction. Although it is unlikely, sympathetic stimulation could be ineffective against hypocapnic airway constriction and still be effective against other constrictor agents. This was not tested in this study. However, β-adrenergic stimulating drugs have been shown to be effective against hypocapnic airway constriction (5, 12). Also the degree of hypocapnia imposed on the LLL was extreme. The constriction produced by this degree of hypocapnia probably produced airway closure since 5% CO_2 produced only a partial relaxation of the constricted airways. Hyperinflation was required to return the airway pressure back to control. However, although a partial dilation of the airways was possible, sympathetic nerve stimulation was ineffective in producing any dilation of airways constricted by hypocapnia. Furthermore, in most of the experiments sympathetic stimulation was initiated as end-expired CO_2 was decreasing and airway pressure was increasing in an attempt to block the hypocapnic airway constrictor response. Although the measurement of pulmonary mechanics was made at an expired CO_2 of approximately 0%, a dose–response curve developed as the end-expired CO_2 decreased. This was particularly apparent in the perfused preparation (Fig. 3) in which end-expired CO_2 changed more slowly than during acute lobar artery occlusion. Not only was the maximum hypocapnic constrictor response not affected by sympathetic stimulation but also the dose–response relationship which developed as end-expired CO_2 decreased did not appear to be affected.

Thus, sympathetic nerve stimulation, although effective against vagally induced bronchoconstriction and effective in producing increased pulmonary vascular resistance did not significantly affect hypocapnic airway constriction. A nonadrenergic inhibitory nervous system has been shown for the conducting airways of the guinea pig and human conducting airway smooth muscle (13) but not for respiratory airway smooth muscle. The results of this study suggest that the sympathetic innervation does not play a role in the control of the respiratory airways. Thus, although these airways may or may not be affected by vagal stimulation, they are probably predominantly controlled by alveolar CO_2 as it affects the pH of the blood perfusing these airways, by humoral agents released from the lungs, and by circulating humoral agents.

Summary. Two series of experiments were conducted to determine the effect of sympathetic nerve stimulation on hypocapnic airway constriction in the isolated left lower lobe (LLL) of the dog anesthetized with sodium pentobarbital. In the first series, hypocapnic airway constriction was produced by lobar artery occlusion. The bronchodilator effect of sympathetic stimulation on hypocapnic airway constriction was compared to the bronchodilator effect of sympathetic stimulation on the constrictor effects of vagal nerve stimulation. In the second series, the LLL was isolated and pump perfused. Hypocapnic airway constriction was produced by reducing the inspired CO_2 from 5 to 0% in O_2. The increase in lobar artery pressure caused by sympathetic stimulation was used as an index of the effectiveness of sympathetic stimulation to the LLL. In neither series did sympathetic stimulation have a significant effect on hypocapnic airway constriction.

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Received February 12, 1980. P.S.E.B.M. 1980, Vol. 164.