Reflex Cardiovascular Depression during Unilateral Lung Hyperinflation in the Dog

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ABSTRACT We have examined whether lung hyperinflation in the anesthetized dog reflexly depresses cardiac output, stroke volume, heart rate, and blood pressure and whether these changes persist for more than a minute. To eliminate any mechanical restriction to venous return and pulmonary blood flow during lung hyperinflation, a model was developed in which all pulmonary artery blood flow and all ventilation were directed to the right lung in dogs with widely open chest and the left lung was hyperinflated before and after left cervical vagotomy. Heart rate, stroke volume, and blood pressure decreased by 24, 20, and 27%, respectively, within 15 s of left lung inflation to 30 cm H_2O. Heart rate increased to preinflation levels by 1 min, but stroke volume and blood pressure remained depressed during lung hyperinflation for at least 15 min. Upon deflation, stroke volume and blood pressure returned to control levels within 1 min. Division of the left vagosympathetic trunk at the neck interrupted all autonomic afferent and efferent nerves of the left lung, but left intact the right vagal sympathetic and parasympathetic afferent and efferent nerves of the heart. After left cervical vagotomy the transient fall in heart rate, stroke volume, and blood pressure during left lung hyperinflation was greatly reduced or eliminated. These results suggest that unilateral lung hyperinflation reflexly depresses heart rate and blood pressure, which are partially compensated with time, and reflexly depresses stroke volume, which persists uncompensated until the lung is deflated. These findings may explain the depressed cardiovascular function observed during regional lung overdistention especially when it occurs during positive pressure ventilation.

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INTRODUCTION

Our interest in reflex cardiovascular effects of lung hyperinflation arose as a consequence of observations that ventilation with positive end-expiratory pressure that hyperinflates the lung, depresses cardiac output beyond that attributable to mechanical obstruction either to venous return or to pulmonary circulation (1–4). To study reflex cardiovascular effects of lung hyperinflation, it is necessary to employ a model in which the direct mechanical effects of lung inflation are eliminated. One model in which the reflex effects of lung hyperinflation have been studied is in dogs during cardiopulmonary bypass. In this model, lung hyperinflation has produced transient decreases in heart rate, blood pressure, and ventricular contractility, decreases that are eliminated by bilateral cervical vagosympathectomy (5–8). The elimination of the lung hyperinflation response with bilateral cervical vagosympathectomy may be the result of interrupting autonomic afferents from the lungs or other intrathoracic viscera or a result of interrupting parasympathetic and sympathetic efferents to the heart and peripheral vessels or perhaps the result of both mechanisms. Furthermore, the overall effect of lung hyperinflation on the cardiac output cannot be studied during cardiopulmonary bypass, and the duration of the known cardiovascular responses to lung hyperinflation has not been fully explored. The purpose of this study was to examine three unresolved questions regarding the cardiovascular effects of lung hyperinflation. (*a*) Does lung hyperinflation reflexly reduce cardiac output and stroke volume in addition to blood pressure, heart rate, and ventricular contractility? (*b*) Does the fall in blood pressure, heart rate, and perhaps cardiac output persist beyond 1–2 min? (*c*) Are these responses reflexly mediated by afferent nerves that originate from receptors within the lung? To examine these questions we have developed an animal preparation in which one lung can be hyperinflated without mechanically ob-

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structing the blood flow returning to the heart or to the other lung, and in which autonomic afferents from the hyperinflated lung can be blocked without interrupting the sympathetic and parasympathetic efferent nerves of the heart.

METHODS

20 mongrel dogs of either sex, weighing 16–25 kg, were studied. 10 were anesthetized with pentobarbital (30 mg/kg) and 10 were anesthetized with chloralose (50–100 mg/kg) and morphine sulfate (2 mg/kg). All were intubated through a tracheostomy with a double lumen endobronchial tube with an inflatable cuff[1] that completely separates right and left lung ventilation. During instrumentation the lungs were ventilated bilaterally a total of 15 ml/kg at 10 breaths/min on a Harvard apparatus sinusoidal pump respirator (Harvard Apparatus Co., Inc., Millis, Mass.). Left and right airway pressures were measured with Statham PM131 transducers (Statham Instruments, Inc., Oxnard, Calif.) connected to each endobronchial tube. A femoral artery and vein were exposed and cannulated. Through the femoral vein two balloon-tipped, flow-directed catheters were placed, one in the pulmonary artery from which pressures and thermal dilution cardiac output determinations were obtained, and the other in the right atrium for pressure measurements. The chest was widely opened through a sternotomy, the left pulmonary artery was carefully exposed, and a ligature loosely applied for subsequent left pulmonary artery occlusion. Through a 1- to 2-cm opening in the pericardium, the left atrial appendage was cannulated. Approximately 150 ml of normal saline were administered after opening the chest, and blood loss was replaced. After surgical preparation and instrumentation were complete, the left pulmonary artery was ligated diverting all pulmonary blood flow to the right lung. At this time all ventilation was directed to the right lung by diverting the left endobronchial tube from the ventilator to atmosphere. Ventilatory rate was adjusted until the PA_{CO_2} was between 38 and 42. Supplemental oxygen was administered in a nonquantitative way if the PaO_2 were <75 mm Hg. Pressures were recorded on a six-channel Grass polygraph recorder (Grass Instruments Co., Quincy, Mass.). Mean vascular pressures were obtained by electronic filtering, and mean right lung pressure was obtained by planimetry. Blood pressure, heart rate, and cardiac output were monitored for at least 30 min and determined to be stable before inflating the left lung. Pressures and heart rate were continuously recorded as the left lung was inflated to 30 cm H_2O by flow from a compressed air line into the left endobronchial tube. Inflation pressure was maintained at 30 cm H_2O by having the compressed air exit port submerged 30 cm below the surface of a water reservoir. Cardiac output was measured singly at 15 s and in triplicate at 1-, 5-, 10-, and 15-min intervals. Peripheral vascular resistance was calculated as mean arterial blood pressure divided by cardiac output, and stroke volume was calculated as cardiac output divided by heart rate. 3 ml of arterial blood were sampled anaerobically before left lung hyperinflation and at 1-, 5-, and 15-min intervals during left lung hyperinflation for assay of pH, PaO_2, and PA_{CO_2}.

Initially, three successive 1-min lung inflations, 15 min apart, were performed in seven dogs to examine the reproducibility of the cardiovascular effects of lung hyperinflation. Because the anesthetic agent might affect both the cardiovascular response to lung inflation and the rate at which the model deteriorates, both pentobarbital and chloralose/morphine anesthesia were employed, and transient changes in cardiovascular function were studied during left lung hyperinflation and deflation. Transection of the left cervical vagosympathetic trunk was performed in 10 dogs. Cardiac output, heart rate, and blood pressure were monitored for 15 min after vagotomy, which was sufficient time to assure that the animal was stable and that heart rate, blood pressure, and cardiac output were not changing. The left lung was then hyperinflated as before vagotomy.

Student's t test for paired data was used to analyze the statistical significance of the cardiovascular changes during lung inflation and deflation and to analyze the significance of the difference between pre- and postvagotomy cardiovascular responses to lung inflation. Student's t test for nonpaired data was used to analyze the significance of the differences between pentobarbital- and chloralose/morphine-anesthetized dogs.

RESULTS

Polygraph tracings of vascular and airway pressures during lung inflation before and after left cervical vagosympathectomy in dogs anesthetized with chloralose/morphine are illustrated in Figs. 1 and 2. A substantial decrease in blood pressure, heart rate, and cardiac output was demonstrated as the left lung, which was isolated from the circulation, was inflated to 30 cm H_2O before vagotomy. This response to left lung inflation was virtually eliminated after vagotomy.

To compare cardiovascular effects of lung inflation before and after vagotomy, it was necessary to establish that cardiovascular responses do not diminish with repeated lung inflations nor with time. Because preliminary studies revealed that maximal cardiovascular effects would occur within 15–30 s (Fig. 1), the left lung was

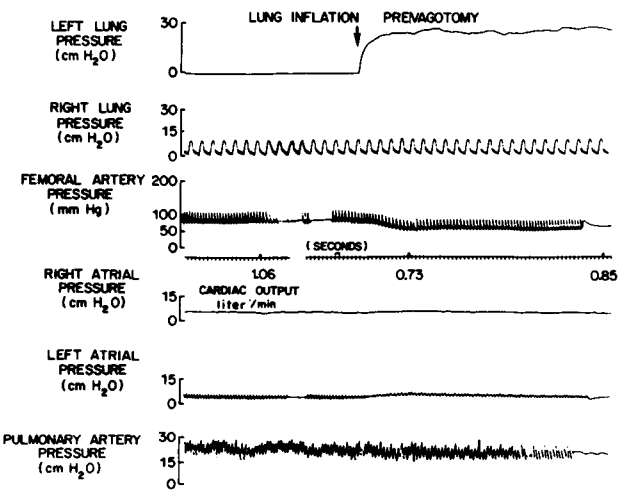

FIGURE 1 A polygraph recording of right and left lung pressure, right and left atrial pressure, systemic and pulmonary artery pressure, and thermal dilution cardiac output before and during 1 min of left lung inflation before vagotomy. The good separation of right and left lung pressures is illustrated.

[1] Kottmeier endobronchial canine tube, 39 FR, Rüsch, West Germany.

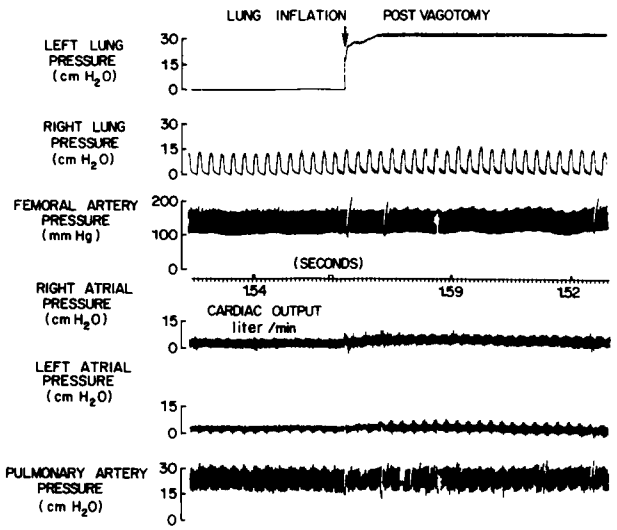

FIGURE 2 A polygraph recording of right and left lung pressure, right and left atrial pressure, systemic and pulmonary artery pressure, and thermal dilution cardiac output before and during 1 min of left lung inflation after left cervical vagotomy.

inflated to 30 cm H_2O for ≅1 min and deflated for 10–15 min on three successive occasions in seven dogs. The maximal changes in cardiac output, heart rate, and blood pressure are shown in Fig. 3. Cardiac output fell 24%, blood pressure fell 18%, and heart rate fell 16% during the first inflation. Changes in cardiac output, blood pressure, and heart rate during subsequent inflations were not significantly different from the reduction during the first inflation. Thus, neither repeated lung inflations nor a 30- to 45-min lapse in time diminishes these cardiovascular responses to lung hyperinflation, and left lung inflation after vagotomy could be repeated within 45 min and compared to lung inflations before vagotomy.

Cardiovascular responses to lung inflation comparing chloralose/morphine and pentobarbital anesthesia are listed in Table I as mean±SE of the means. During a control period before left lung hyperinflation, cardiac output was slightly higher in the pentobarbital group, but this difference was not statistically significant. Heart rate was significantly higher in the pentobarbital group ($P < 0.05$), and stroke volume, blood pressure, and peripheral vascular resistance were not significantly different between the two groups during the control period. Maximal changes in cardiac output, heart rate, stroke volume, blood pressure, and peripheral vascular resistance during left lung hyperinflation were not significantly different between the groups. Upon deflation, cardiac output, stroke volume, and blood pressure returned to preinflation levels within 1 min in the chloralose/morphine-anesthetized dogs. Although early transient responses were not measured in the pentobarbital-anesthetized dogs, measurements taken 10 min after deflation revealed that cardiac output, stroke volume, heart rate, and blood pressure had returned to control levels. Thus, the cardiovascular effects of left lung inflation are completely reversible. Because the extent to which these cardiovascular parameters changed during left lung hyperinflation and deflation was the same irrespective of the anesthetic agent, the data were grouped for subsequent analysis.

Prevagotomy lung inflation. Altogether, 15-lung inflations were performed in 10 dogs for 15 min, and an average response for each dog was obtained. Left airway pressure increased from 0.1±0.26 cm H_2O to 33.1±1.44 cm H_2O. Changes in cardiac output, heart rate, stroke volume, and pressures are shown in Figs.

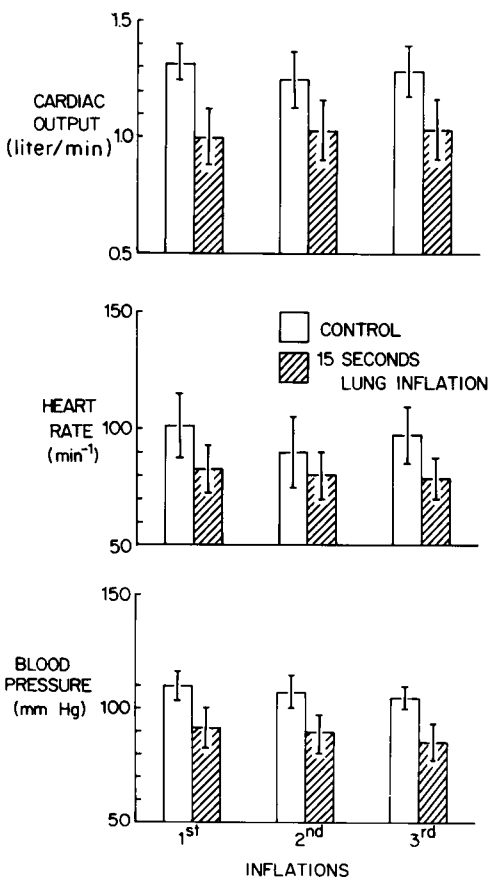

FIGURE 3 Changes in cardiac output, heart rate, and blood pressure from control measurements during three consecutive lung inflations at 15 s in seven dogs. Vertical bars represent SE of the mean. Control measurements before the second and third lung inflations are not significantly different from control measurements preceding the first. Cardiac output, blood pressure, and heart rate fall significantly ($P < 0.05$) with each inflation. Changes in cardiac output, heart rate, and blood pressure during the second and third inflations are not significantly different from the changes during the first inflation.

TABLE I

*Cardiac Output, Heart Rate, Stroke Volume, and Blood Pressure during Inflation and Deflation of the Left Lung in Four Dogs Anesthetized with Chloralose and Morphine and in Six Dogs Anesthetized with Pentobarbital**

	Control	Inflation‡					Deflation			
Min		0.25	1	5	10	15	0.25	1	5	10
Cardiac output, *liter/min*										
Chloralose	1.26 ±0.07	0.80§ ±0.05	1.01§ ±0.05	1.03§ ±0.08	0.99§ ±0.05	1.02§ ±0.04	1.23 ±0.12	1.17 ±0.07	1.20 ±0.06	—
Pentobarbital	1.41 ±0.12	0.82§ ±0.11	1.08§ ±0.10	1.14§ ±0.13	—	1.18§ ±0.08	—	—	—	1.52 ±0.13
Heart rate, *beats/min*										
Chloralose	117 ±22	92§ ±16	112 ±15	112 ±18	112 ±17	112 ±18	122 ±12	110 ±19	112 ±18	117 ±20
Pentobarbital	149‖ ±7	111§ ±11	130§ ±9	145 ±7	—	142 ±7	—	—	—	156 ±12
Stroke volume, *ml*										
Chloralose	11.9 ±1.6	9.1§ ±1.0	9.6§ ±1.2	10.1 ±1.9	9.4§ ±1.3	10.0 ±1.6	10.6 ±1.6	11.8 ±1.9	11.7 ±1.6	—
Pentobarbital	9.6 ±0.8	7.7§ ±1.1	8.5§ ±0.8	7.9§ ±0.9	—	8.5§ ±0.7	—	—	—	9.8 ±0.9
Blood pressure, *mm Hg*										
Chloralose	104 ±3	83§ ±10	88§ ±12	91§ ±11	89§ ±7	89§ ±5	94§ ±8	103 ±10	99 ±3	104 ±5
Pentobarbital	100 ±6	68§ ±9	89§ ±8	94§ ±7	—	93§ ±6	—	—	—	100 ±4

* Values are means±SEM.

‡ Inflation of left lung to 30–35 cm H_2O.

§ Significantly different when compared to pre inflation control, $P < 0.05$.

‖ Significantly different when pentobarbital control is compared to chloralose control, $P < 0.05$.

4–7 as mean±SE of the means. Cardiac output fell 40% below control at 15 s and increased to 22% below control at 1 min (Fig. 4). The cardiac output did not change further after 1 min. This fall in cardiac output was due both to a 24% fall in heart rate and a 22% fall in stroke volume. Heart rate subsequently increased to 11% below the control rate by 1 min and was not different from the control rate thereafter. Stroke volume increased to 13% below the control level by 1 min but did not change thereafter and remained significantly below the control level ($P < 0.05$). This reduction in stroke volume accounts for nearly all the reduction in cardiac output after 1 min of left lung inflation. Blood pressure fell 27% at 15 s as peripheral vascular resistance increased 38% (Fig. 5). Blood pressure rose to 13% below the control measurement at 1 min as a result of the rise in cardiac output as peripheral vascular resistance actually fell from 38% above the control value to 27% above the control value. Blood pressure and peripheral vascular resistance did not change significantly thereafter. Pulmonary artery pressure did not change significantly as pulmonary vascular resistance increased ≅31% (Fig. 6). Left and right atrial pressure increased 1.5 and 2.5 cm H_2O, respectively, and right lung pressure also increased a similar amount, by 1.6 cm H_2O (Fig. 7).

Before left lung inflation Pa_{O_2} was 219 mm Hg±54 SEM, ranging from 78 to 511; Pa_{CO_2} was 38.5 mm Hg±1.7, ranging from 32 to 42; and the pH was 7.29±0.03, ranging between 7.25 and 7.39. Pa_{O_2} did not change significantly at 1, 5, and 15 min (245±61, 214±48, and 223±41 mm Hg); Pa_{CO_2} fell to 33.4±1.4 mm Hg ($P < 0.001$) at 1 min and subsequently increased toward the control level (33.6±2.3 and 35.2±1.8). The pH increased to 7.32±0.03 ($P < 0.005$) at 1 min and was not significantly different from the control value at 15 min, 7.29±0.04.

Postvagotomy lung inflation. After section of the left cervical vagosympathetic trunk, control cardiac output and blood pressure were not significantly different from prevagotomy control values (Figs. 4 and 5). After left vagotomy, control heart rate was higher, 152 vs. 138 beats/min ($P < 0.025$) and control stroke volume was lower, 9.54 vs. 10.37 ml ($P < 0.05$) compared to con-

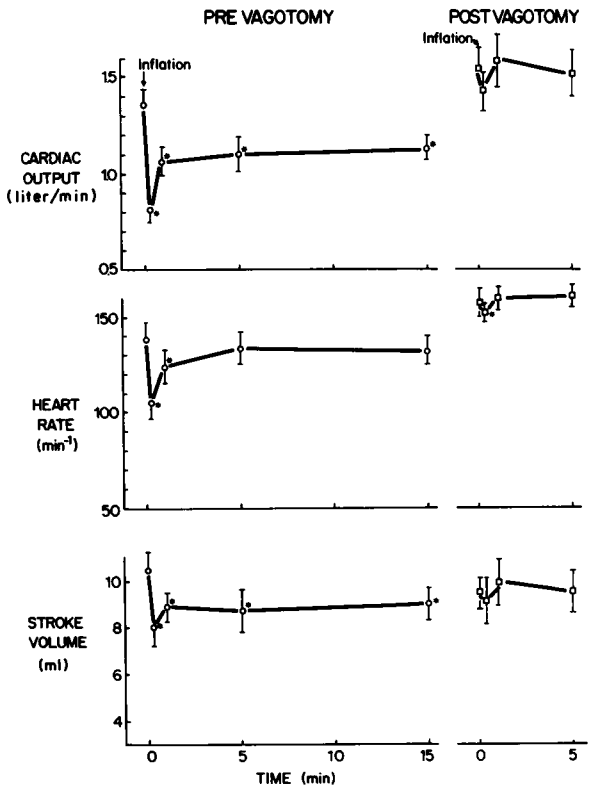

FIGURE 4 Cardiac output, heart rate, and stroke volume during control conditions and lung inflation, both before and after left cervical vagotomy. Vertical bars represent standard error of the mean. (*) represents a significant change ($P < 0.05$) from the preinflation value.

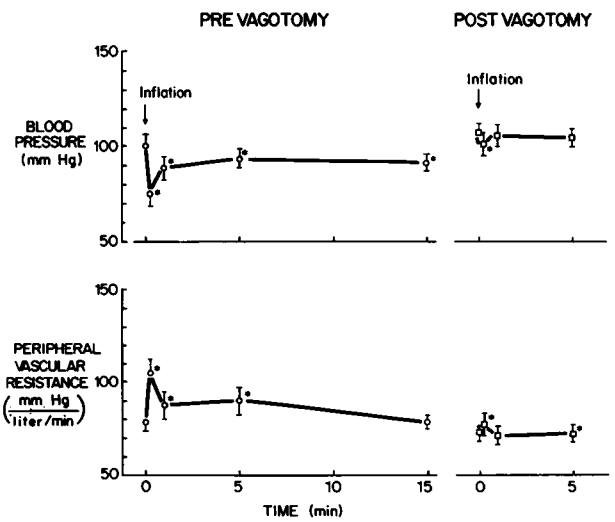

FIGURE 5 Blood pressure and peripheral vascular resistance during control conditions and during lung inflation, both before and after left cervical vagotomy. Vertical bars represent SE of the mean. (*) represents a significant change ($P < 0.05$) from the preinflation value.

trol values before left vagotomy. 16 lung inflations were performed in 10 dogs for 5 min, and an average response for each dog was obtained. Left airway pressure increased from 0.3±0.32 to 35.5±1.05 cm H_2O during left lung inflation, which was not significantly different from prevagotomy left lung pressure changes. Cardiac output and stroke volume did not change significantly during left lung hyperinflation after left vagotomy. Blood pressure and heart rate decreased very slightly at 15 s of lung hyperinflation, 108–101 mm Hg ($P < 0.025$) and 158–153 beats/min ($P < 0.05$), and both returned to postvagotomy control values within 1 min. Changes in cardiac output, heart rate, stroke volume, blood pressure, and peripheral vascular resistance during 15 s, 1 and 5 min of left lung inflation postvagotomy were significantly less than those changes during 15 s, 1 and 5 min of left lung inflation prevagotomy.

DISCUSSION

Reflex depression of stroke volume and cardiac output during lung hyperinflation. To investigate the effects of lung hyperinflation on stroke volume and cardiac output and still avoid the mechanical effects of lung inflation we developed a model in dogs with widely opened chests in which the left lung could be inflated without mechanically restricting venous return or altering pulmonary blood flow to the right lung. In this model, left lung inflation to ≅30 cm H_2O caused a prompt fall in heart rate, cardiac output and blood pressure as shown in Figs. 1, 3, and 4. The fall in cardiac output is because of a fall in stroke volume as well as a fall in heart rate. Stroke volume reduction cannot be explained by reductions in ventricular filling

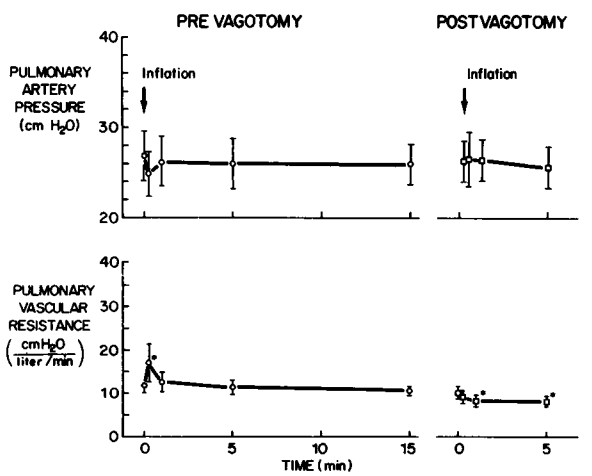

FIGURE 6 Pulmonary artery pressure and pulmonary vascular resistance during control conditions and during lung inflation, both before and after left cervical vagotomy. Vertical bars represent SE of the mean. (*) represents a significant change ($P < 0.05$) from the preinflation value.

as neither left nor right mean atrial pressure fell (Fig. 7). Nor can stroke volume reduction be explained by an increased afterload on the right or left ventricle since systemic blood pressure actually fell and pulmonary artery pressure did not change. Absence of both preload and afterload changes that would result in reduced stroke volume indicates that the decrease in stroke volume during unilateral lung hyperinflation is not due to a direct mechanical effect on the heart.

The fall in heart rate and blood pressure during unilateral lung hyperinflation are of a similar magnitude to that reported by Salisbury et al. (7), Daly et al. (6), and Glick et al. (8) with bilateral lung hyperinflation during cardiopulmonary bypass. The threshold of inflation pressure required to produce these cardiovascular depressing responses has been reported between 10 and 20 cm H_2O (5, 6), and the extent to which heart rate and blood pressure fall increases in proportion to the increase in inflation pressure (6).

Peripheral vascular resistance in our study increased during lung hyperinflation. These results differ from the findings of Salisbury et al. (7) and Glick et al. (8) but they are not necessarily contradictory. Both Glick and Salisbury measured peripheral vascular resistance directly while blood flow was maintained constant. In our study, peripheral vascular resistance was estimated indirectly by dividing mean systemic arterial pressure by cardiac output while cardiac output was allowed to change. These two methods of estimating peripheral vasomotor tone are not comparable when the cardiac output is changing.

Although right airway pressure did not change during left lung hyperinflation, pulmonary vascular resistance of the right lung increased. The increase in pulmonary vascular resistance is proportional to that expected as a consequence of reduced blood flow through the right lung (9) although pulmonary vascular vasoconstriction cannot be excluded. Because cardiac output decreased and pulmonary vascular resistance increased, pulmonary artery pressure did not change.

Duration of lung hyperinflation effects. The blood pressure, heart rate, and ventricular contractility response to lung hyperinflation has been previously noted to have reached a maximum and be returning toward preinflation values within the inflation period of 20–60 s (5–8). That this was systemic baroreceptor compensation was demonstrated by Ott and Shepherd (10), who in baroreceptor denervated rabbits, showed that the fall in hind limb vascular resistance during lung hyperinflation could persist beyond 2 min. We also observed that within 1 min heart rate, blood pressure, and cardiac output were returning toward control levels which is compatible with a baroreceptor response. Heart rate returned completely to control values but did not exceed them. Yet, stroke volume and blood pressure remained depressed significantly

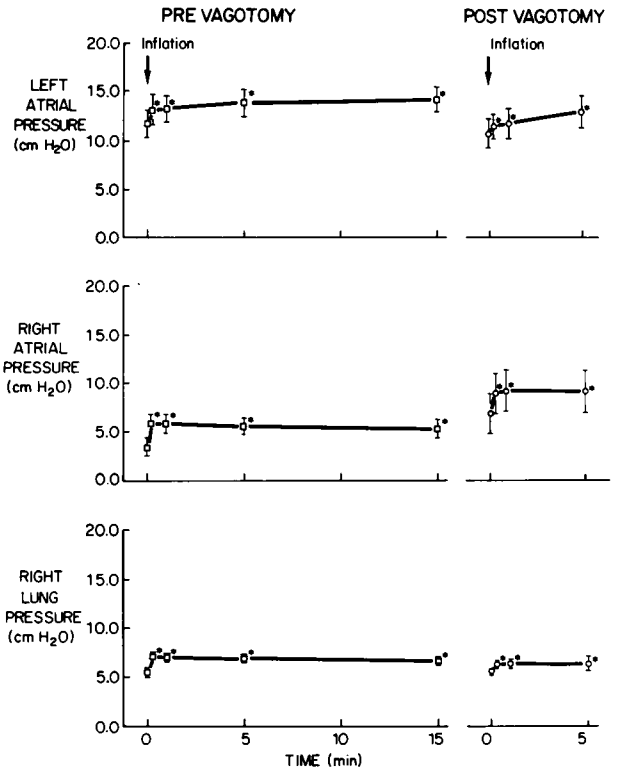

FIGURE 7 Left atrial, right atrial, and right lung pressure during control conditions and during lung inflation, both before and after left cervical vagotomy. Vertical bars represent SE of the mean. (*) represents a significant change ($P < 0.05$) from the preinflation value.

below control values for at least 15 min. The return of heart rate to control levels does not reflect complete compensation since sustained depression of blood pressure should have evoked tachycardia through the systemic baroreceptors. Upon deflation of the lung cardiac output, stroke volume, and blood pressure returned to preinflation control levels within 1 min, indicating that the stimulus that led to depressed cardiac output, stroke volume, and blood pressure during hyperinflation had persisted the entire 15 min (Table I) and that the sustained depression was not merely a function of time in a deteriorating model. The depression in stroke volume and blood pressure was not a function of changes in arterial oxygen or carbon dioxide tension or arterial pH. Arterial oxygen tension did not change. Arterial P_{CO_2} fell and pH rose transiently, but both returned to or toward control levels with time, whereas the depression in stroke volume remained fixed. The changes observed in the arterial P_{CO_2} and pH are expected transiently after a fall in cardiac output in the absence of any changes in metabolic CO_2 production. The long duration of the cardiovascular response indicates that the mechanism mediating the response is slowly adaptive, and the quick reversibility

suggests a neural rather than circulating humoral mechanism mediating the response.

Afferent limb of the lung hyperinflation reflex. There are three known afferent receptors in the lung all of which can be stimulated by mechanically distorting the lung. The identification and localization of these afferent receptors has been reviewed by Dawes and Comroe (11), Paintal (12), and by Coleridge and Coleridge (13). These are the stretch receptors first reported by Adrian (14), which when stimulated evoke a modest increase in blood pressure and heart rate (15), the irritant receptors which evoke no known cardiovascular responses (16), and C-fiber receptors which when stimulated evoke a marked bradycardia and hypotension (15). Thus, all of the observed cardiovascular effects of unilateral lung hyperinflation, the fall in heart rate, blood pressure, and stroke volume are likely the result of stimulation of C-fiber receptors. C-fibers carried in the vagi arise from receptors in the great veins, myocardium, coronary arteries, pericardium, and aorta (13, 17, 18) as well as in the lung, and hyperinflation of one or both lungs distorts any of these structures and stimulates C-fibers outside the lungs to elicit the observed cardiovascular responses. However, one recent study suggests that 85% of the normal cardiopulmonary depressor nerve traffic in the vagosympathetic trunks is carried by the right vagus and that 85% of the nerve traffic originating from cardiac receptors that evoke the Bezold-Jarisch reflex is carried in the right vagus (19). Hence, most of the normal afferent and(or) efferent depressor nerves from mechanoreceptors chemoreceptors in the heart and great vessels remain intact in our model even after the left vagosympathetic trunk is cut. Yet, almost all of reflex responses to left lung hyperinflation were eliminated by left cervical vagosympathectomy. We can conclude that the great majority and perhaps all of the afferent receptors involved with the reflex initiated by left lung distention must arise within the left lung or left hemithorax. The slight response to left lung hyperinflation that remains after the left cervical vagus has been cut suggests that a portion of the receptors stimulated by hyperinflation may transmit impulses in afferent fibers that traverse spinal nerves or suggests that receptors outside the left hemithorax are stimulated.

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