Circulatory responses from lung inflation in anesthetized dogs

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METHODS

All experiments were performed on dogs (weight 14–24 kg) anesthetized with 100 mg/kg chloralose dissolved in polyethylene glycol (100 mg chloralose/ml polyethylene glycol). Further doses (10–20 mg/kg) were given as required to maintain a steady state of light anesthesia.

To permit independent inflation of each lung, a tracheal divider (Kottmeier endobronchial canine tube, Rusch, W. Germany) was inserted through a tracheotomy incision and placed so that each limb lay in each main bronchus. An inflatable cuff at the lower end of the divider effectively separated air flow in the two main bronchi. One lung at a time was inflated with air from a compressed air source, the pressure of which was set by placing an overflow tube under water to the appropriate depth. Because of the anatomy of the dog’s tracheobronchial tree, it was not possible to obtain a completely air-tight seal of the tracheal divider with the tracheal bifurcation without obstructing the upper lobe bronchi, and at high inflation pressures some air leaked back up the trachea. This was automatically replaced to maintain a constant inflation pressure. This technique meant that the volume inflating the lung was not known.

When required, the lungs were ventilated by intermittent positive pressure applied to each side of the tracheal divider by means of a double-barreled Harvard respiratory pump. Arterial blood gases and pH were measured at intervals using standard glass electrode systems (Instrumentation Laboratories Inc.). Acidemia was corrected by intravenous administration of molar sodium bicarbonate to bring arterial pH within the range 7.35–7.40. If \( \text{Pa}_2 \) fell below 70 mm Hg, oxygen was added to the inspired air. When the dog was ventilated artificially, \( \text{Pa}_2 \) was kept between 35 and 40 mm Hg by adjusting the stroke of the pump (rate 18/min).

A Grass polygraph recorded blood pressures (using Statham P23 Gb transducers), chest wall movements (using an air filled corrugated rubber pneumograph connected to a Statham transducer), and an electrocardiogram.

Control of Input From Arterial Baroreceptors

To prevent modification of the responses to lung inflation by a change in the stimulus to aortic and carotid baroreceptors, in seven dogs the aortic receptors were denervated and the pressure perfusing the carotid baroreceptors was held constant. In these dogs the right lung was inflated, and since...
it was necessary to preserve vagal afferents from it and vagal efferents to the heart, the right vagus nerve was not cut and the baroreceptors at the right subclavian angle (23) were denervated by cutting the right aortic nerve at its junction with the superior laryngeal nerve (15). The aortic nerve was distinctly seen at the superior laryngeal-vagal junction in four out of the seven dogs. In the remaining three dogs, a distinct aortic nerve was not seen, so the tissue in the angle between the superior laryngeal nerve and the vagus nerve was cut and the superior laryngeal nerve was dissected away from the vagus for about 0.5 cm. The left cervical vagosympathetic trunk was cut; this procedure interrupted both the left aortic nerve and the afferent nerves from the left lung. The activity of the carotid sinus baroreceptors was controlled by perfusing the distal ends of the common carotid arteries at constant nonpulsatile pressure with blood obtained from the proximal end of one of the common carotid arteries (5). Carotid sinus pressure was measured using a cannula inserted through a lingual artery.

The completeness of the denervation of the aortic baroreceptors was inferred from the fact that aortic chemoreceptors were no longer active; injections of 100 μg of nicotine bitartrate or 500 μg sodium cyanide into the right atrium did not cause respiratory or heart rate responses until at least 15 s after injection when nicotine or cyanide reached the carotid bodies through delay paths.

Vasomotor responses were assessed by measuring perfusion pressure changes in a hindlimb perfused through the femoral artery by a Sarns roller pump at constant flow using blood obtained from a common carotid artery. To prevent changes in perfusion pressure occurring as a result of changes in blood flow along collateral vessels as systemic arterial pressure changed, a cuffed catheter was passed up a femoral artery to the aortic bifurcation and was distended with 2 ml saline. With the balloon distended and the limb perfusion pump stopped, the pressure in the femoral artery rapidly fell to below 20 mm Hg, indicating the absence of significant anastomoses with the systemic circulation.

### Lung Inflation in Open-Chest Dogs

In this group of experiments, the chest was opened widely in the 5th left intercostal space and the responses were tested to inflating the lungs with different pressures.

In some of these animals, the effects were tested on the responses to lung inflation of occluding the pulmonary artery supplying the inflated lung either by ligature or by inflating a balloon on the end of a transvenous catheter.

### Lung Perfusion

With the chest open in the 5th left intercostal space, the left pulmonary artery was perfused at constant flow by a Harvard pulsatile pump using heparinized blood obtained from a donor dog. The blood leaving the perfused lung was collected and returned to the pump either from cannuulas tied in the pulmonary veins (3 dogs) or by tying the pulmonary vein-arterial junctions, cutting the pulmonary veins to allow pulmonary venous blood to flow into the thoracic cavity, and then draining the blood into a reservoir (11 dogs). In two dogs in which the pulmonary veins had been cannulated, the chest was closed in layers around the cannulas so that the dog could resume spontaneous respiration and respiratory responses could be studied.

#### Lung Denervation by Brief Inhalation of Air and Steam

In some dogs, pulmonary afferent endings or nerves were destroyed by inhalation of steam (18). The dogs were ventilated by the respiratory pump, and steam at 100°C was directed into the tracheal divider to mix with the air inflating one lung for three normal breaths.

### RESULTS

#### Arterial Blood Gas and pH Changes During Inflation

In seven dogs, samples of arterial blood were withdrawn from a short cannula inserted into the abdominal aorta through a femoral artery. Blood was collected before and at 5-s intervals during lung inflation and analyzed for PO₂, PCO₂, and pH. The results show little or no changes in these variables for 10 s after the onset of apnea. Fifteen seconds after the onset of apnea, PAO₂, PACO₂, and pH changed from their control values by −8 mm Hg (SE ± 1.6), + 3.5 mm Hg (SE ± 1.0) and −0.023 units (SE ± 0.011), respectively. As the apnea continued there was a progressive change in the arterial blood gases and pH. To minimize any responses which may have occurred as a result of changes in the arterial blood, responses to lung inflation were assessed only up to the 15th s of inflation.

#### Respiratory Responses

In all experiments in which respiratory responses were studied (24 dogs), lung inflation to all pressures tested (5-40 cm H₂O) resulted in apnea. These experiments include two dogs in which the lung was artificially perfused and the chest was closed. In the dogs with a normal pulmonary circulation and uncontrolled baroreceptors, the average duration of apnea during inflation of one lung to 5 cm H₂O pressure was 20 s (range 14–30 s). At higher inflation pressures, the duration of apnea was not determined; it usually persisted for as long as the lung remained inflated (15–20 s).

#### Circulatory Responses

Procedures usually resulting in tachycardia during lung inflation, inflation of either lung to 10–40 cm H₂O in spontaneously breathing dogs with baroreceptors not controlled. The typical response to inflation of the lung with moderate pressures was an increase in heart rate (Fig. 1). In 28 lungs in 14 dogs, tachycardia was obtained at one or more inflation pressures; in one dog inflation of either lung to any pressure consistently resulted in bradycardia.

There was usually a small fall in arterial blood pressure which was greater at higher inflation pressures. The average decreases in mean arterial pressure at 10, 15, 20, 30, and 40 cm H₂O inflation pressure were 3.2, 4.6, 6.7, 10.3, and 25 mm Hg, respectively.

In five lungs in three dogs, the effects of lung inflation were determined before and after directing steam into the air inflating the lung for three breaths. This procedure abolished or greatly reduced the heart rate responses from lung
inflation, but did not consistently affect the blood pressure changes (Table 1). After inflation of steam by one lung, responses from the contralateral lungs were not affected until after that lung also had been denervated by steam.

**Inflation of Either Lung to 10-30 cm H2O with Chest Open.** In 6 dogs, 10 lungs were inflated with 10-30 cm H2O before and after opening the chest widely in the 5th left intercostal space. There was no significant difference in the heart rate responses obtained with the chest open from those obtained with the chest closed. There was usually a slightly larger fall in arterial blood pressure in the open-chest experiments (Table 2).

In nine dogs, the effects were determined of occluding the left pulmonary artery on the responses to inflating that lung. The left pulmonary artery was occluded in four dogs by a ligature and in two dogs by inflating a balloon on the end of a long transvenous catheter. Tachycardia occurred in response to lung inflation in both dogs in which the pulmonary artery was occluded by balloon and in two of the dogs in which it was occluded by a ligature. In these experiments heart rate increased by an average of +19 beats/min (range, +9 to +23) from an average control value of 132 beats/min (range 115-130). Mean arterial pressure changed by an average of −7.5 mm Hg (range, −18 to +2) from an average control value of 154.5 mm Hg (range, 141-191). In two of the dogs in which the pulmonary artery was occluded by a ligature, bradycardia occurred in response to inflation with 20 cm H2O pressure. Heart rate decreased by −39 and −21 beats/min from control values of 135 and 147 beats/min. Mean arterial pressure decreased by −15 and −6 mm Hg from control values of 122 and 146 mm Hg.

**Inflation of Right Lung to 10-20 cm H2O in Spontaneously Breathing Dogs with Chest Unopened and Arterial Baroreceptor Input Controlled (Heart Rate and Vasomotor Responses).** Inflation of the right lung (right vagus intact) to 10-20 cm H2O pressure resulted in tachycardia and small vasomotor responses. There was usually a small vasocstriction obtained at one or more of the lower inflation pressures tested (e.g. Fig. 2). At 15 cm H2O inflation pressure, the average change in vascular resistance of the first two tests in each dog was an increase of +3.9% (range −1.2 to +13.0). This change was significantly different from the control values (P < 0.02). Vasomotor responses at other inflation pressures were not statistically significant. The changes in heart rate and vascular resistance in all seven dogs at different inflation pressures are shown in Fig. 3.

The lack of large consistent vasomotor responses to lung inflation was shown not to be due to the limb vessels being incapable of responding, because a large step decrease in carotid perfusion pressure immediately resulted in an increase in vascular resistance of 115% (mean, range 86-160). Vasomotor responses to lung inflation were not consistently influenced by setting vascular resistance at different levels by perfusing the carotid arteries at different pressures. Although the control level of limb perfusion pressure was reflexly changed from 194 to 123 mm Hg (flow constant) by increasing carotid perfusion pressure, the average change in limb perfusion pressure on lung inflation remained the same. With carotid pressure low (mean 85 mm Hg; range

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**Table 1. Effects of steam inflation on responses to unilateral lung inflation with 20 cm H2O pressure**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before steam</td>
<td>After steam</td>
</tr>
<tr>
<td>1 R</td>
<td>66 +30</td>
<td>89 −1</td>
</tr>
<tr>
<td>L</td>
<td>90 +30</td>
<td>86 −5</td>
</tr>
<tr>
<td>2 R</td>
<td>91 +23</td>
<td>81 −3</td>
</tr>
<tr>
<td>J</td>
<td>108 +34</td>
<td>120 0</td>
</tr>
<tr>
<td>L</td>
<td>111 +27</td>
<td>99 0</td>
</tr>
<tr>
<td>Mean</td>
<td>93.2 +32.4</td>
<td>95.6 0</td>
</tr>
<tr>
<td>SE</td>
<td>+8.0 +5.5</td>
<td>+6.7 +2.4</td>
</tr>
</tbody>
</table>

Changes in heart rate and mean arterial pressure were calculated by comparing values obtained between the 5th and 15th s of inflation with those obtained during 30 s immediately before inflation. Chest closed, baroreceptors not controlled.

**Table 2. Effects of opening chest widely in fifth left intercostal space on responses of heart and mean arterial pressure to inflation of one lung with 20 cm H2O pressure**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Change</td>
</tr>
<tr>
<td>4 L</td>
<td>162 +12</td>
<td>152 +10</td>
</tr>
<tr>
<td>R</td>
<td>162 +30</td>
<td>136 +34</td>
</tr>
<tr>
<td>5 L</td>
<td>105 +21</td>
<td>120 −6</td>
</tr>
<tr>
<td>R</td>
<td>102 +36</td>
<td>117 +17</td>
</tr>
<tr>
<td>6 R</td>
<td>72 +18</td>
<td>126 +42</td>
</tr>
<tr>
<td>7 R</td>
<td>111 +15</td>
<td>114 +12</td>
</tr>
<tr>
<td>6 R</td>
<td>102 +10</td>
<td>121 +5</td>
</tr>
<tr>
<td>R</td>
<td>96 +18</td>
<td>132 +36</td>
</tr>
<tr>
<td>9 L</td>
<td>117 +30</td>
<td>144 +21</td>
</tr>
<tr>
<td>R</td>
<td>116 +16</td>
<td>133 +9</td>
</tr>
</tbody>
</table>

Control and change refer to observations made during the 0.5-s control period immediately before inflation and the changes from the control values between the 5th and 15th s of inflation. The only significant changes after opening the chest was that there was a larger fall in mean arterial pressure during inflation (P < 0.05 for paired observations).
FIG. 2. Inflation of right lung to 20 cm H₂O with constant input from arterial baroreceptors. Right aortic and left vagus nerves cut; carotid arteries perfused at constant pressure. Hindlimb perfused at constant flow with abdominal aorta occluded at bifurcation. RESP = chest wall movements recorded from pneumograph. ṖCAr = carotid artery perfusion pressure mm Hg; ṖFEM = pressure in perfused hindlimb, mm Hg; Psys = systemic arterial blood pressure recorded in brachial artery, mm Hg; bottom traces of ECG and 1-s time and event markers. Note that in this experiment both heart rate and arterial blood pressure increased during spontaneous inspiration and during lung inflation.

65-103 mm Hg), inflation of the right lung with 20 cm H₂O pressure caused an average increase in heart rate of +22 beats/min (range +15 to +30) from a control value of 175 beats/min (range 117-210). With carotid pressure high (mean 154 mm Hg; range 135-178 mm Hg), lung inflation caused an average increase in heart rate of +28 beats/min (range +12 to +43) from a control level of 105 beats/min (range 75-135). At the low carotid pressure, lung inflation caused femoral perfusion pressure to increase by +3.0% (range -2.5 to +8.6) from its control value of 194 mm Hg (range 143-259). At the high carotid pressure, femoral perfusion pressure again increased by an average of +3.0% (range -4.9 to +16.9) from a control level of 123 mm Hg (range 108-142).

In three dogs tested the responses to inflation were greatly reduced or abolished following steam inhalation. For example, inflation with 20 cm H₂O before steam caused changes in heart rate of +34, +33, and +15 beats/min, and after steam, -3, +2, and +2 beats/min. Before steam there were increases in hindlimb vascular resistance of 7, 10, and 8% and after steam an increase of 1% and decreases of 2 and 4%.

Procedures usually resulting in bradycardia during lung inflation. Inflation of right lung to 30-40 cm H₂O in spontaneously breathing dogs with chest unopened and arterial baroreceptor input controlled (heart rate and vasomotor responses). Inflation to 40 cm H₂O always resulted in bradycardia, sometimes very marked (Figs. 3, 4). Responses at 30 cm H₂O were less definite, although in four out of seven dogs there was a marked bradycardia. At 30-40 cm H₂O inflation pressure, the vasomotor responses were variable. A marked vasodilatation occurred in two dogs, but little change occurred in the other five. As was found at lower inflation pressures the vasomotor responses were not consistently modified by changing the initial levels of vascular resistance by setting carotid pressures at different values.

After steam inhalation, heart rate responses were reduced. In three dogs inflation of the right lung to 40 cm H₂O resulted in an average decrease in heart rate before steam of 89 beats/min, and after steam, of 19 beats/min.

Inflation of lung when the pulmonary circulation...
TABLE 3. Responses of heart rate and mean arterial blood pressure to inflation of lung with 20 cm H2O pressure immediately before and immediately after hyperinflation with 40 cm H2O pressure

<table>
<thead>
<tr>
<th>Dog</th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before hyperinflation</td>
<td>After hyperinflation</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Change</td>
</tr>
<tr>
<td>10 L</td>
<td>66</td>
<td>+12</td>
</tr>
<tr>
<td>R</td>
<td>69</td>
<td>+27</td>
</tr>
<tr>
<td>11 L</td>
<td>72</td>
<td>+17</td>
</tr>
<tr>
<td>R</td>
<td>74</td>
<td>+13</td>
</tr>
<tr>
<td>12 L</td>
<td>97</td>
<td>+11</td>
</tr>
<tr>
<td>R</td>
<td>91</td>
<td>+23</td>
</tr>
<tr>
<td>13 L</td>
<td>129</td>
<td>+15</td>
</tr>
<tr>
<td>R</td>
<td>126</td>
<td>+24</td>
</tr>
<tr>
<td>14 L</td>
<td>114</td>
<td>+42</td>
</tr>
<tr>
<td>R</td>
<td>133</td>
<td>+15</td>
</tr>
<tr>
<td>Mean</td>
<td>97.3</td>
<td>+19.9</td>
</tr>
<tr>
<td>SE</td>
<td>±8.5</td>
<td>±3.0</td>
</tr>
</tbody>
</table>

Control and change refer to observations made during the 30-s control period immediately before inflation and the changes from the control values between the 5th and 15th s of inflation. Dogs 10–14 without control of baroreceptors; dogs 27–32 baroreceptors controlled. Responses of heart rate to inflation with 20 cm H2O immediately after hyperinflation are significantly different from those obtained before hyperinflation. Using paired observations, for dogs 10–14, P < 0.005; for dogs 27–32, P < 0.05.

The responses were not related to a rise in pulmonary artery perfusion pressure because in four experiments when left pulmonary artery perfusion pressure was changed in a single step from 15 cm H2O (range 7–25) to 77 cm H2O (range 68–88) by changing the rate of the perfusion pump, heart rate never changed by more than 6 beats/min (avg change, +0.5 beats/min) and systemic arterial blood pressure never changed by more than 4 mm Hg (avg change 0). In Fig. 6 the absence of a response when pulmonary artery flow was changed is contrasted with the bradycardia and hypotension occurring during lung inflation.

FIG. 4. Inflation of right lung to 40 cm H2O with constant input from arterial baroreceptors. Same dog as in Fig. 2. Conventions as in Fig. 2. Note that there was a fall in femoral artery perfusion pressure during inflation and again during period of hyperpnea after release of inflation.

FIG. 5. Changes in heart rate and mean systemic arterial pressure resulting from inflation of perfused (left) lung to different pressures. Continuous ventilation of normally perfused (right) lung. Results of means and standard errors from averages of responses in 14 dogs. Changes calculated by comparing values obtained between 5th and 15th s of inflation with control values during 30-s period immediately before inflation.

OF THAT LUNG IS ARTIFICIALLY PERFUSED. In 12 out of 14 dogs with open chests and artificially perfused left lungs, inflation of the perfused lung with pressures of 10–40 cm H2O resulted in bradycardia and hypotension (Fig. 5). The responses increased with increasing inflation pressures. 

In two of the dogs the chest was closed around the perfusion cannulas and spontaneous breathing resumed. Infla-
varying the conditions. Because inflation of a lung may result in inhibition of respiratory efforts. However, the factors responsible for changing the reflex activity of the lung can be considered and discussed in relation to results reported by previous investigators.

**Reflex Nature of Responses**

There can be no doubt that positive pressure inflation of a lung alters the afferent nervous activity from that lung. However, the observed reflex responses may not necessarily be solely due to this change in nervous activity because there were several other concomitant changes in the circulation: 1) during the period of reflex apnea during lung inflation, there was a change in arterial blood Po2, Po4, and pH. 2) The rise of intrathoracic pressure during positive-pressure lung inflation is known to impede venous return to the heart and thereby lower cardiac output and arterial pressure. Only one lung was inflated at a time in an attempt to minimize this effect, but nevertheless some obstruction to blood flow is likely to have occurred, particularly at the higher inflation pressures. 3) In those experiments in which arterial blood pressure fell during inflation, there would have been a changed stimulus to arterial baroreceptors. 4) Lung inflation may also cause a changed stimulus to nerves ending in the heart and great vessels.

The effects of a changed stimulus to chemoreceptors are likely to be small because the time courses of the responses to inflation and the changes in blood gas and pH are different. The maximum change in heart rate occurred within 5 s of the onset of inflation, whereas changes in blood gas and pH were insignificant up to this time and remained small for 15 s after onset of inflation. Since no measurements were made from records after 15 s of inflation, it is unlikely that chemoreceptors made a significant contribution to the responses. Chemoreceptors cannot have influenced responses at all in experiments with cut aortic nerves and perfused carotid arteries (shown by injection into the right atrium of nicotine or cyanide) or in the perfused lung experiments in which ventilation of the normally perfused lung continued unchanged during inflation of the artificially perfused lung.

The experiments which are most vulnerable to criticism are those in which a lung was inflated in dogs with closed chests and baroreceptors not controlled. In these experiments arterial blood pressure usually fell, and there must have been a considerable change in the stimulus to many cardiovascular nerve receptors. However in some experiments in which heart rate increased arterial pressure did not fall and sometimes it even increased. Also steam inhalation, which denervates only the lungs (18), was effective in preventing tachycardia from occurring during lung inflation. Nevertheless, the possibility that in some experiments there may have been some secondary effects due to circulatory obstruction cannot be ruled out, and for this reason the series of experiments was done in which the input from arterial baroreceptors was held constant. The results in these experiments of inflating a lung with moderate pressures were essentially similar to those obtained in experiments without baroreceptor control. However, the re-

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**TABLE 4. Responses to inflation of perfused (left) lung with 30 cm H2O pressure before and after steam inhalation by that lung**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before steam</td>
<td>After steam</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>15</td>
<td>120 -24</td>
<td>192 0</td>
</tr>
<tr>
<td>16</td>
<td>108 -20</td>
<td>105 +2</td>
</tr>
<tr>
<td>16*</td>
<td>78 -66</td>
<td>196 0</td>
</tr>
<tr>
<td>20</td>
<td>123 -22</td>
<td>100 -6</td>
</tr>
<tr>
<td>24</td>
<td>93 -18</td>
<td>99 -3</td>
</tr>
<tr>
<td>Mean</td>
<td>104.4 -30.0</td>
<td>126.0 -1.4</td>
</tr>
<tr>
<td>SE</td>
<td>+8.3 +9.1</td>
<td>+17.1 +1.4</td>
</tr>
</tbody>
</table>

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**Fig. 6. Inflation of perfused lung to 30 cm H2O and changing flow of blood through lung. Records of left pulmonary artery perfusion pressure (mm Hg), femoral arterial blood pressure (mm Hg), ECG and 1 s time marker. Numbers above record of pulmonary artery pressure are of blood flow (ml/min); numbers above ECG are of heart rate (beats/min). Results show bradycardia and hypotension in response to lung inflation but no response to changing blood flow.**

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**Discussion**

Inflation of either lung in all experiments consistently resulted in inhibition of respiratory efforts. However, the effects on the circulatory system were variable and different responses could usually be obtained in the same dog by varying the conditions. Because inflation of a lung may cause widespread alterations in the circulation, it is important to be clear to what extent the responses recorded were the direct reflex effects of stimulation of nerves ending in the airways and lungs. Then the factors responsible for changing the reflex activity of the lung can be considered and discussed in relation to results reported by previous investigators.
LUNG INFLATION REFLEX

is that a change in the stimulus to nerves ending in other intrathoracic sites may have affected the responses. It is difficult to control the input from nerves ending in the heart and great vessels. Maintaining constant pressures in all these areas, even if it were possible without altering the reflex activity of the lungs, would not ensure that afferent nerve activity remained constant because, during lung inflation, many nerves may have an increased afferent discharge due to distortion, even when there is a lower distending pressure due to impaired filling. For example, an increased discharge in a left atrial receptor during lung inflation is illustrated in an earlier paper (18). The technique of steam inhalation was used to show that responses arose from stimulation of nerves ending in the lungs and not elsewhere in the thorax. This technique has been shown not to affect nerves ending elsewhere than the lungs, so the fact that responses to inflation were abolished following steam implies that responses from the heart and great vessels cannot have made a major contribution to the overall changes. Steam inhalation is a much more useful localizing procedure than nerve section because it would completely denervate the lung including receptors with afferent fibers which run in the sympathetic nerves as well as the vagi (21). Also if it is desired to cut the vagal branches to lungs and not the heart, a deep dissection is required to identify the pulmonary nerves as they run over the trachea and bronchi. Some nerves may be missed, some cardiac nerves may be damaged, and deep dissections in the thorax may modify the reflex responses from the lungs.

It is likely that the decrease in heart rate in all these experiments was a direct reflex response to lung inflation. It certainly could not have been due to increased baroreceptor stimulation. In experiments in which the response to inflation changed from an increase to a decrease in heart rate, it is unlikely that the stimulus to receptors outside the lungs would be different. Also the responses were abolished after steam was inhaled by the lung.

In the perfused lung experiments the fall in arterial blood pressure was also a reflex effect because circulatory obstruction is unlikely in these experiments and this fall in pressure, unlike the hypotension in the closed chest dogs, did not occur after steam inhalation.

In the preparations in which vasomotor responses were studied, the input from arterial baroreceptors was controlled. The limb was isolated by inflating a balloon in the aorta near the bifurcation. This balloon effectively obstructed the flow of blood into the common iliac and median sacral arteries. The absence of significant collateral flow to the perfused limb was seen by the rapid fall in arterial pressure when the perfusion pump was stopped. This perfusion system did not prevent normal vasomotor responses from occurring as seen by brisk responses to changes in carotid perfusion pressure. The reflex vasomotor responses to lung inflation were small compared with those obtained by changing carotid pressure. There was no significant degree of vasodilatation at moderate inflation pressures and only occasionally at the higher pressures.

On the basis of the evidence discussed above, therefore, it is reasonable to conclude that, with the exceptions of the fall in arterial pressure at lower inflation pressures and the increase in heart rate during hyperinflation in dogs with normally perfused lungs, all the responses reported were the direct reflex effects of stimulation of intrapulmonary nerves.

Factors Changing Reflex Activity of Lungs

The normal reflex activity of the lung must become altered during or following hyperinflation or artificial perfusion. Since different responses can be obtained in any dog, these variations could not have been due to peculiarities of some of the dogs. The variations must have been due to variable predominance of one reflex mechanism over another.

It has been known for a long time that there are receptors within the lungs capable of causing either bradycardia or tachycardia, since injection of drugs into the pulmonary circulation or stimulation of afferent pulmonary nerves results in either an increase or a decrease in heart rate (1, 4, 14). The lung has a very rich afferent innervation of all its structures (16, 31), and many of the nerves are known to be stimulated by inflation. The main nerve endings likely to be involved are a) low threshold slowly adapting pulmonary stretch receptors, which are thought to lie in and around airways and be responsible for the Hering-Breuer inflation reflex (3), b) "irritant" receptors in large and small airways, which are rapidly adapting and transiently stimulated by greater degrees of stretch (23, 28), c) deflation receptors, which may have a decreased stimulation on inflation, although the receptors described by Paintal (25, 26) designated as "J" receptors appear not to be stimulated significantly on deflation unless the animal was first given an injection of phenyl diguanide, d) endings of the very many unmyelinated fibers travelling from the lungs, the function of most of which are unknown, but some of which have been shown to be stimulated by hyperinflation (8). In the present experiments although the steam technique permits the localization of the receptors involved to the lungs, it does not identify which of the many types of intrapulmonary receptors are likely to be involved in each response.

The variable responses at 5 cm H2O inflation pressure can be explained in terms of the central and reflex components of sinus arrhythmia (2). In those experiments in which heart rate slowed during inflation with 5 cm H2O the rate remained at the end-expiratory level; i.e., the slowing was due to the absence of inspiratory tachycardia. It is possible, therefore, that the degree of inflation was sufficient to inhibit inspiration, but was not great enough to excite sufficiently the intrapulmonary receptors responsible for reflex tachycardia. If this is so, then either the receptors responsible for tachycardia are different from those responsible for the Hering-Breuer reflex or low stimulation of a receptor causes apnea and a more intense stimulation of the same receptor also results in tachycardia.

Bradycardia resulting from hyperinflation may be due to stimulation of another type of receptor with a high threshold. However, what happens on inflation with 40 cm H2O or artificial perfusion to change the responses to lower pressure.
inflation from being a tachycardia to bradycardia is far from clear. There are basically two ways in which the reflex activity can be altered: a) the receptors responsible for the tachycardia response have a lower threshold and in some way become less sensitive after overstretching or artificial perfusion, or b) inflation with higher pressures or artificial perfusion causes receptors which normally have a higher threshold to become active at lower pressures.

Simply opening the chest did not cause the response to inflation with the lower pressures to be consistently changed, although in open-chest dogs the responses to inflation were more variable. This increased variability could have been due to increased distension of the lungs because of the absence of the restraining effect of the chest wall. Interrupting the pulmonary circulation did not usually modify the response, although in two dogs it did. In these two experiments and in the perfused lung experiments the change in the response to lung inflation from tachycardia to bradycardia may have been associated with handling the lung or, in the perfusion experiments, perfusing it with heparinized blood from a different dog. The change in the response was not reversed in the two dogs in which the chest was closed after connecting the perfusion circuit and spontaneous breathing resumed.

It is known that the reflex activity of the lung is altered when the lung is congested or edematous, resulting in rapid shallow breathing (7, 19). Congestion, pneumothorax, and microembolism increase the activity of "irritant" receptors (23, 28), and the activity of some lung receptors also can be modified by inhalation of some anesthetics agents (9, 28).

It is conceivable, in the present study, that the reflex activity of artificially perfused lungs could be altered in this way, but the changes which followed a single, short inflation to 40 cm H₂O require a different explanation. It is well known that a deep breath temporarily increases the compliance of the lungs (3), so inflation with 20 cm H₂O after hyperinflation might produce a similar distension to that previously obtained at 40 cm H₂O and induce the reflex responses usually occurring with the higher pressure. However, if the change in the response were simply the result of increased compliance, then inflation with even lower pressures should have resulted in an increase in heart rate. This was not so. A further possibility is that hyperinflation expands areas of atelectasis allowing stretch receptors in those areas to respond to inflation, and this might also reduce the effects of mechanical obstruction. However, these possibilities seem unlikely for several reasons: repeated inflation with 20 cm H₂O should be sufficient to prevent areas of atelectasis from occurring. Inflation of a lung in which the areas of atelectasis have been removed should result in qualitatively similar responses as when less of the lung is subjected to the same stimulus. Also, following hyperinflation there was a larger fall in arterial pressure in response to inflation with lower pressures. It is likely, therefore, that the change in the response is due to a change in the reflex activity of the lungs.

Relevance of Results to Previous Studies

The main new observations described in this paper are 1) that different cardiovascular responses can be obtained in the same animal, depending on the experimental conditions; 2) responses to inflation are modified following hyperinflation or artificial perfusion; and 3) reflex vasodilatation does not occur in response to inflation of normally perfused lungs with moderate pressures.

Tachycardia in response to lung inflation was described previously by Anrep et al. (1) and Daly et al. (10, 13). Bradycardia and hypotension occurring in response to lung inflation were described previously by Glick et al. (17) and Salisbury et al. (27). The results obtained from the present experiments help to account for some of the conflicting responses described in earlier studies. Thus, although Daly and co-workers (10, 13) reported tachycardia and vasodilatation occurring from lung inflation, they never obtained the two responses in the same preparation. Tachycardia occurred on inflating normally perfused lungs in closed-chest dogs, whereas a small vasodilation occurred in preparations involving complex perfusion circuits (11, 12). It seems probable that had it been possible to study heart rate responses using the latter preparations, bradycardia would have been observed. Also in experiments described by others in which depressor responses resulted from lung inflation, it is noted that high inflation pressures were used or the normal perfusion of the lung was altered (17, 20, 27). The results of the earlier studies, therefore, are not incompatible with the conclusions of this study. That is, the normal response to inflation of a normally perfused lung with moderate pressures is tachycardia with, if anything, a small vasoconstriction and bradycardia and vasodilatation only occur on hyperinflation or when the normal reflex activity of the lung is in some way altered.

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