Several studies have suggested the possibility of a causal relationship between changes in lung volume (LV) and changes in pulmonary vascular resistance (PVR). In general, data indicate that an increase in LV above normal results in increased PVR. On the other hand, there is relatively little information on the effect of decreasing LV below normal. Cloetta was the first to suggest that decreased LV might also result in elevated PVR, giving a "U-shaped" curve relating resistance to LV, but his data were not conclusive. Burton and Patel recently presented data indicating that this relationship held for the saline-perfused lung of the open-chest rabbit. Simmons and Hemingway observed markedly increased PVR following induction of pneumothorax in closed-chest dogs, also consistent with Cloetta’s hypothesis.

Because the effect of both increased and decreased LV on PVR had never been investigated simultaneously in the intact animal, the present study was undertaken.

Methods

Ten experiments were conducted on mongrel dogs (8.6 to 27.4 Kg.) anesthetized with 25 mg./Kg. of sodium pentobarbital intravenously, with small additional doses as needed. Normal ventilation was maintained with a Starling respiration pump (positive-pressure breathing), small doses of intravenous succinylcholine chloride being given for muscle relaxation. The inspired gas was pure oxygen to prevent hypoxia and its effects on cardiac output and pulmonary vascular resistance (PVR). The lungs were hyperinflated with a pressure of approximately 30 cm. H₂O every 15 minutes, to prevent distribution abnormalities and resultant changes in acid-base status. Pressures were measured with electrical pressure transducers from an arbitrary zero 14 cm. above the dog’s back. Differential pressures were determined directly, using differential transducers. Mean pressures were obtained by electrical integration. The following pressures were determined directly: (1) pulmonary artery pressure (PAP), using a cardiac catheter inserted through the external jugular vein; (2) left atrial or pulmonary venous pressure (LAP), using a cardiac catheter inserted through the femoral artery; (3) pulmonary vascular pressure gradient (PVPG = PAP-LAP), using both cardiac catheters and a differential pressure transducer; (4) intratracheal pressure (ITP); (5) intrapleural pressure (IPP), using a Harvard pleural cannula inserted through the fourth interspace to the right of the sternum; (6) transpulmonary pressure (TPP = ITP-IPP); (7) distending pulmonary artery pressure (DPAP = PAP-IPP), which is the effective distending pressure or "transmural pressure" of major pulmonary arteries; and (8) distending left atrial pressure (DLAP = LAP-IPP), the effective pressure distending the left atrium or pulmonary veins. Mean femoral artery pressure (FAP) was measured with a mercury manometer, and the experiment was discontinued if a drop of over 25 per cent occurred.

Cardiac output (CO) was measured by the dye-dilution technique, using cardio-green dye and a Colson cuvette densitometer. Duplicate determinations differed less than 5 per cent, on the average. Withdrawn blood was reinfused to minimize blood-volume changes.

The following determinations were made anaerobically on arterial blood: (1) pH at 37 C, with a Beckman model GS pH meter; (2) pCO₂, calculated from pH and CO₂ content (Van Slyke) by the Henderson-Hasselbalch equation; and (3) oxygen saturation by a standard spectrophotometric technique.

Pulmonary vascular resistance was calculated in arbitrary units by dividing PVPG (in cm. H₂O) by CO (in L./min./Kg.).
Measurements were made at zero end-expiratory pressure (zero EEP) and at smaller and larger lung volumes obtained with negative or positive end-expiratory pressures of 15 cm of water at the same respiratory rate and tidal volume (fig. 1). Thirty minutes were allowed for equilibration after each change in EEP. The order of measurements at zero, negative, and positive EEP was varied in different experiments to obtain an orthogonal system and eliminate effects of the supine position and duration of anesthesia. Examination of the final data revealed no consistent tendency for changes in PVR with time.

Eight experiments were conducted using all three end-expiratory pressures and lung volumes. Two more experiments were conducted in which six sets of measurements were made at alternate zero and negative EEP. One of these is graphically presented in figure 2.

In evaluating the responses, changes were calculated from the values at zero EEP, and the significance of the changes was determined by standard statistical techniques.

The change in LV or functional residual capacity (FRC), when starting either negative or positive EEP, was calculated by the following equations:

With zero EEP:

$$C = \frac{\text{Tidal vol. in cc.}}{\text{TPP}_{\text{exp}} - \text{TPP}_{\text{insp}}}$$  \hspace{1cm} (1)

At negative or positive EEP:

$$\Delta \text{FRC} = C \times (\text{EEP}_z - \text{EEP}_{\text{zero}})$$  \hspace{1cm} (2)

In these equations, (C) signifies lung compliance, and (TPP_{exp}) and (TPP_{insp}) signify transpulmonary pressure at the end of expiration and inspiration.

Results

The principal results are summarized in table 1 and are graphically plotted against changes in LV in figure 3.

Pulmonary Vascular Resistance

Of 14 measurements of PVR at decreased LV, 12 were higher than at normal LV, one was unchanged, and one was lower. The mean increase was 24 per cent. In both experiments with rapid alternation between zero and negative EEP, PVR was higher at the smaller lung volume each of the six times it was determined (fig. 2). At increased LV, PVR increased in every case; average increase was 18 per cent.

Cardiac Output

With negative EEP, CO increased in 12 of 13 cases; the mean increase was statistically significant. CO decreased in every case at positive EEP.

Pulmonary Vascular Pressures

PAP and LAP decreased significantly with negative EEP and increased significantly.
with positive EEP, as one would expect. However, the effective distending pressure (or transmural pressure), which is the difference between absolute vascular pressure and intrapleural pressure, did not change in the same manner. With negative EEP, mean DPAP and DLAP both increased, the former significantly. In the case of positive EEP, there was an increase in DPAP and a slight decrease in DLAP, but neither of these changes was statistically significant and therefore neither could account for the increased PVR at increased or decreased LV.

The mean pressure gradient between pulmonary artery and pulmonary vein increased significantly with both negative and positive EEP.

**Functional Residual Capacity**

Mean decrease in FRC with negative EEP was 32 per cent of the predicted normal of 25 ml./Kg.; mean increase with positive EEP was 75 per cent.

**Intratracheal Pressure**

Mean intratracheal pressure was 3.3 cm. H$_2$O for positive-pressure breathing at zero EEP. With negative EEP, this decreased to -7.2, and with positive EEP it rose to +17.4. Measurements were therefore made under conditions of slight positive-pressure breathing at zero EEP, high positive-pressure breathing at positive EEP, and negative-pressure breathing at negative EEP.

**Femoral Artery Pressure**

There were no significant differences between FAP measured at zero and at negative EEP. On changing to positive EEP, there was a slight drop in seven experiments and a small increase in one. The mean change was not statistically significant.

**Arterial pH**

Arterial pH dropped an average of 0.07 units (0.02 to 0.10) during positive EEP breathing and rose an average of 0.06 units (0.00 to 0.12) during negative EEP in four experiments. These changes are consistent with the metabolic acidosis associated with positive-pressure breathing (unpublished ob-

**Figure 3**

Summary of results. Changes ($\Delta$) in pulmonary vascular resistance (PVR), cardiac output (CO), distending or transmural pulmonary artery pressure (DPAP), left atrial pressure (DLAP), and pressure gradient from artery to vein are plotted for decreased, normal, and increased FRC. The mean per cent changes in FRC are indicated by solid circles.

Arterial pCO$_2$

Arterial pCO$_2$ did not change significantly, decreasing an average of 2.4 mm. Hg with positive EEP and 0.8 mm. Hg with negative
**Table 1**

Summary of Results (Ten Experiments)*

<table>
<thead>
<tr>
<th></th>
<th>PVR (mm Hg)</th>
<th>CO (ml/min/kg)</th>
<th>PAP (cm H2O)</th>
<th>LAP (cm H2O)</th>
<th>DPAP (cm H2O)</th>
<th>DLAP (cm H2O)</th>
<th>Gradient (cm H2O)</th>
<th>IPP (cm H2O)</th>
<th>ITP (cm H2O)</th>
<th>FRC (cc)</th>
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<tr>
<td><strong>Mean</strong></td>
<td>92.6</td>
<td>91.9</td>
<td>14.3</td>
<td>6.5</td>
<td>16.2</td>
<td>10.4</td>
<td>7.8</td>
<td>-2.8</td>
<td>+3.3</td>
<td>473</td>
</tr>
<tr>
<td><strong>S. E.</strong></td>
<td>15.1</td>
<td>9.7</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td>1.3</td>
<td>0.6</td>
<td>0.4</td>
<td>45</td>
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<tr>
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<td>14</td>
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<td>14</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>15</td>
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<tr>
<td><strong>Change with decreased lung volume (negative EEP)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>+31.9</td>
<td>+17.8†</td>
<td>-1.9†</td>
<td>+4.3†</td>
<td>+6.5†</td>
<td>+2.9†</td>
<td>+3.0†</td>
<td>-8.2†</td>
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<td>-32%†</td>
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<tr>
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<td>0.7</td>
<td>0.9</td>
<td>0.8</td>
<td>1.6</td>
<td>0.7</td>
<td>0.6</td>
<td>0.3</td>
<td>7.4</td>
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<tr>
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<td>14</td>
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<td>11</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>13</td>
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<tr>
<td><strong>Change with increased lung volume (positive EEP)</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>+168.1</td>
<td>-30.4†</td>
<td>+11.7†</td>
<td>+5.4†</td>
<td>+4.3</td>
<td>-1.6</td>
<td>+4.4†</td>
<td>+6.8†</td>
<td>+14.1†</td>
<td>+75%†</td>
</tr>
<tr>
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<td>33.4</td>
<td>7.9</td>
<td>1.8</td>
<td>1.6</td>
<td>2.3</td>
<td>2.2</td>
<td>1.0</td>
<td>0.6</td>
<td>1.5</td>
<td>26.8</td>
</tr>
<tr>
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<td>6</td>
<td>6</td>
<td>7</td>
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</tr>
</tbody>
</table>

*CO = cardiac output; PAP = pulmonary artery pressure; LAP = left atrial pressure; gradient = PAP-LAP; PVR = gradient/C0; DPAP = effective distending pressure, pulmonary artery; DLAP = effective distending pressure, left atrium; IPP = intrapleural pressure; FRC = functional residual capacity; S.E. = standard error of mean; N = number of measurements.

†Changes in FRC stated in per cent of normal predicted FRC.

The observed increases in PVR could not be due to the mechanical effects of positive-pressure breathing or the resultant changes (i.e., CO) and therefore must be ascribed to changes in the geometry of some part of the pulmonary vasculature associated with the change in lung volume itself. It is possible that neurohumoral factors may condition the response.

Of special interest is the effect of negative and positive EEP on PVR. With increased LV, PVR rose in each of eight experiments to almost triple the control value. Of the 14 measurements made in 10 experiments at decreased LV, PVR rose in 12, decreased in one, and remained unchanged in one; the mean increase, approximately 25 per cent, was statistically significant. These data indicate that pulmonary vascular resistance increases with both increased and decreased LV under the conditions of these experiments. These results were not due to decreased distending pressures of pulmonary vessels secondary to changes in pulmonary blood flow (i.e., CO) and therefore must be ascribed to changes in the geometry of some part of the pulmonary vasculature associated with the change in lung volume itself. It is possible that neurohumoral factors may condition the response.
LUNG VOLUME AND PULMONARY RESISTANCE

in CO, since positive-pressure breathing primarily affects the systemic circulation and has no direct effect on the pulmonary circulation, and since no significant changes in the large-vessel distending pressures resulted from changes in CO.

Our data indicate that the increase in PVR with decreased LV is considerably less than that following increased LV. However, the change in LV with positive EEP was more than double that with negative EEP, so that a greater change in PVR might be expected on this basis alone. Calculating the increase in PVR per unit change in LV, the effect of positive EEP is still much greater than that of negative EEP. Part of this remaining difference may be ascribed to the fact that positive-pressure breathing was used in this study rather than spontaneous breathing.

Decreased venous return and decreased flow at increased LV results in lowering of the distending pressure of pulmonary vessels and increasing of their resistance to flow. With spontaneous breathing, the respiratory effect on flow at increased LV would be reversed, and resistance would therefore probably be lower than our observed values.

Increased PVR with decreased LV in this study is considerably less than that noted for a comparable degree of lung collapse following pneumothorax, probably because of opposite effects of the procedures on venous return and cardiac output and consequent opposite effects on effective distending pressure of the pulmonary vessels. The effect on PVR, independent of the artifacts of either experiment, might lie somewhere between the values observed in this study and in the pneumothorax study.

Since PVR rose with both increased and decreased LV, even though distending pressures of major pulmonary vessels were constant or increased, one must ascribe the increased PVR to either: (1) decreased distending pressure of small vessels lying deep in the lung parenchyma and not exposed to IPP; (2) decreased distensibility of pulmonary vessels, which might then have a smaller diameter in spite of increased distending pressure; or (3) a change in vessel geometry which would increase the turbulence of pulmonary blood flow and thereby increase resistance. Nor is it necessary to postulate the same one of these mechanisms for increased PVR at both decreased and increased LV.

There is evidence that the increased PVR at increased LV is due to a decrease in caliber of small vessels of the lung because of a decrease in their effective distending pressure. Schleier performed calculations indicating that the major PVR is in the small vessels. Irwin et al. presented confirming histological evidence and demonstrated that these vessels lie in alveolar septa and are therefore exposed to alveolar pressure. One can demonstrate that for either normal respiration or positive-pressure breathing, the transmural or distending pressure in these vessels and their diameters must decrease as the lung distends. This is borne out by the observation that the volume of blood in the smaller lung vessels decreases as LV increases.

There is evidence for two mechanisms by which PVR might rise with decreased LV. First, Burton and Patel demonstrated a change in geometry of arterioles ("gnarliness") with lung collapse, which appears...
capable of causing increased resistance to flow in this area. Secondly, Macklin and Howell, Permutt, and Proctor demonstrated that the volume of blood in the larger pulmonary vessels decreases as LV decreases below normal, indicating a probable decrease in diameter and increased resistance to flow. Both arteriolar gnarliness and large-vessel collapse might contribute to increased PVR at decreased LV; there are no data by which to judge their relative importance. If decreased diameter were the factor increasing resistance at decreased LV, a U-shaped curve of PVR might be described if one considered overall PVR as the sum of resistance in large and small vessels (fig. 4).

As Burton and Patel pointed out, increased PVR at below-normal LV could be due either to passive changes in geometry of pulmonary vessels or to reflex increases in vasomotor tone. That the changes are passive is suggested by the effect of pneumothorax on PVR and by the open-chest data of Burton and Patel, since their ligation of the pulmonary artery in all probability interrupted the nervous supply to the vessels.

As expected, cardiac output decreased with positive EEP, the usual result of increased intrathoracic pressure in the anesthetized dog. The fact that CO was higher with negative EEP and negative-pressure breathing (mean intrathoracic pressure = —10.5 cm. H2O) than at zero EEP should not be taken to indicate that negative-pressure breathing in itself increases CO. It is likely, instead, that the slight positive-pressure breathing at zero EEP leads to reduction in CO, as compared with spontaneous breathing, while negative-pressure breathing has no effect on CO.

Burton and Patel have pointed out two reasons for confusion in evaluating effects of various procedures on PVR. These are: (1) the fact that PAP has been used as a measure of the driving force of blood across the pulmonary circulation, while this measure should in fact be pressure drop from pulmonary artery to vein, i.e., PVPG; and (2) the fact that the pressure passively distending pulmonary vessels has been assumed to be the intravascular pressure, rather than the effective distending pressure or transmural pressure. This study points out a third possible source of confusion, namely, variation in lung volume from one study to another.

**Summary**

Ten experiments were conducted on anesthetized dogs ventilated with a Starling pump and breathing oxygen. While tidal volume, respiratory rate, and arterial pH and pCO2 were kept constant, lung volume was varied by using either a negative, zero, or positive end-expiratory pressure, leading to average changes in lung volume of —32, 0, and +75 per cent. Pulmonary vascular resistance (PVR) increased with either decreased or increased lung volume, indicating that the relationship between resistance and lung volume is a U-shaped curve. Since the transmural distending pressures of large pulmonary vessels either increased or remained unchanged during these procedures, changes in PVR cannot be ascribed to changes in systemic circulatory dynamics, such as cardiac output.

It was noted that cardiac output increased with negative end-expiratory pressure (effectively, negative-pressure breathing) and decreased with positive end-expiratory pressures (effectively, positive-pressure breathing), as previously reported. A hypothesis is presented for explaining the U-shaped curve relating resistance and lung volume.

**References**


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