The Effect of Vascular Volume on Positive End-Expiratory Pressure-Induced Cardiac Output Depression and Wedge-Left Atrial Pressure Discrepancy

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Positive end-expiratory pressure (PEEP) is effective in improving arterial oxygenation and decreasing intrapulmonary shunt in patients with the adult respiratory distress syndrome [9, 12]. PEEP can also cause a significant reduction in cardiac output [6, 8, 13, 15] and decrease in oxygen delivery [12]. The decrease in cardiac output may be due to impaired venous return [1, 7, 14], pulmonary vascular compression [5, 6, 12], or left ventricular dysfunction [8, 13] and may be reversed by acute volume expansion [14, 17]. When cardiac output falls with PEEP, pulmonary capillary wedge pressure may not accurately reflect left atrial pressure [5, 8, 12] and, thus, is a poor monitor of volume requirements in patients. Six baboons were studied to determine more accurately the effect of PEEP on cardiac output and the relation between wedge and left atrial pressure under conditions of acute and chronic volume expansion.

METHOD

Six healthy adult male baboons (Papio anubis), 22–29 kg in weight, were sedated intramuscularly with phencyclidine hydrochloride (Sernylan, 1 mg/kg). Catheters were positioned under fluoroscopic control in the right atrium, left atrium, pulmonary artery (flow-directed balloon catheter [16]), and abdominal aorta. A balloon-tipped catheter was placed in the midesophagus to monitor intrathoracic pressure. Urine was collected through a Foley catheter, and rectal temperature was monitored with a Telethermometer. After introduction of a cuffed endotracheal tube, the baboons were paralyzed with pancuronium bromide (Pavulon, 0.1 mg/kg) and were ventilated with a fixed-volume Harvard respirator, 10 ml/kg, at a rate to maintain a constant PaCO₂ between 30 and 40 mm Hg (6–9/min) during a 30-min stabilization period. Respirator settings were not changed thereafter.

The effects of increasing levels of PEEP were determined in four conditions in each baboon. For each experimental condition, the following set of data was obtained. Phasic and electronic mean arterial (BP), pulmonary artery (PA), pulmonary capillary wedge (PCWP), left atrial (LAP), central venous (CVP), and esophageal pressures were measured by Statham transducers and were recorded on a Sanborn polygraph. Cardiac output (C.O.) was determined by the indocyanine green dye dilution technique. Arterial and mixed venous blood gases and hemoglobin were measured, and oxygen delivery was calculated from the product of cardiac output and arterial oxygen content. Intrapulmonary shunt (Qs/Qt) was calcu-
lated using the standard shunt equation, and pulmonary vascular resistance (PVR) was calculated from

$$PVR = [(\overline{PAP} - \overline{LAP}) \times 80],$$

where $\overline{PAP}$ = mean pulmonary artery pressure, $\overline{LAP}$ = mean left atrial pressure, and C.O. = cardiac output.

In each experimental condition, after initial basal measurements (0 cm H$_2$O PEEP), end-expiratory pressure was increased in 5-cm H$_2$O increments to 20 cm H$_2$O using a magnetic valve on the expiratory line and then was returned to 0 cm H$_2$O PEEP. Data was collected after a 15-min stabilization period at each new level of PEEP.

**Normovolemia.** With the animals supine, sedated, and paralyzed, the effects of increasing levels of PEEP were determined. No fluid was given, and the volume of blood removed for analysis was replaced with an equal volume of Ringer's lactate solution. Small amounts of heparinized D5W were used to maintain catheter patency. Both ureters were then ligated through a small midline incision in order to prevent diuresis with subsequent fluid administration.

**Acute hypervolemia.** This was produced by rapid (50 ml/min) infusion of Ringer's lactate until left atrial pressure reached 20 mm Hg. The rate of fluid administration was decreased to 15 ml/min and continued at that rate while the effects of increasing levels of PEEP were determined. A total of 3800 ± 120 ml of Ringer's lactate was given in 150 min. During the entire day, 4600 ± 150 ml of Ringer's lactate was given, and 2100 ± 400 ml of D5W was used to maintain catheter patency. After completion of the studies, each animal was given additional phencyclidine and pancuronium and was maintained on the ventilator until the next day. No additional fluid was given and the baboons were maintained supine and were turned side to side and suctioned every 2-4 hr.

**Chronic fluid overload.** Twenty-four hours after ureteral ligation and rapid fluid administration, five animals were alive, and the effects of increasing levels of PEEP were determined in the supine position.

**Functional hypovolemia.** Each of the five animals was then placed upright in a chair to produce venous pooling and functional hypovolemia. Transducer positions were adjusted to correspond to the level of the atria and at least 30 min were allowed for stabilization. The effects of increasing levels of PEEP in upright paralyzed baboons 24 hr after ureteral ligation and rapid fluid administration were determined.

The effect of PEEP in each experimental condition was determined by comparing the values obtained at 5, 10, 15, 20, and 0 cm H$_2$O PEEP with the initial zero PEEP value for that condition. Statistical significance was determined using the paired t-test.

**RESULTS**

**Normovolemia**

Cardiac output fell as the level of PEEP increased and was significantly depressed at 10, 15, and 20 cm PEEP. At 20 cm PEEP, cardiac output had decreased 30%, but blood pressure was unchanged (Table 1). PEEP caused intrathoracic pressure to rise as reflected by the rise in esophageal pressure. Central venous and left atrial pressure rose proportional to the rise in esophageal pressure (Fig. 1), and there was no change in right atrial or left atrial transmural filling pressure (CVP – esophageal and LAP – esophageal) (Fig. 4). Pulmonary capillary wedge pressure increased over more than other intrathoracic pressures at 15 and 20 cm PEEP and no longer accurately reflected left atrial pressure. At 20 cm PEEP, wedge pressure was 3 mm Hg higher than left atrial pressure ($P < 0.05$). Pulmonary vascular resistance rose markedly at each level of PEEP at which cardiac output fell (Fig. 5). Upon removal of PEEP, esophageal and intravascular pressures and pulmonary vascular resistance returned to
TABLE 1

Effect of PEEP in Supine Normovolemic Baboons

<table>
<thead>
<tr>
<th>Level of PEEP (cm H₂O)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.O. (liters/min)</td>
<td>3.0 ± 0.2*</td>
<td>2.8 ± 0.3</td>
<td>2.5 ± 0.1**</td>
<td>2.3 ± 0.1***</td>
<td>2.1 ± 0.2***</td>
<td>2.3 ± 0.2*</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>137 ± 7</td>
<td>138 ± 5</td>
<td>139 ± 3</td>
<td>143 ± 4</td>
<td>141 ± 5</td>
<td>137 ± 4</td>
</tr>
<tr>
<td>Mean PA (mm Hg)</td>
<td>17 ± 2</td>
<td>19 ± 1</td>
<td>24 ± 1**</td>
<td>29 ± 2**</td>
<td>40 ± 2***</td>
<td>16 ± 1</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>7.8 ± 0.9</td>
<td>10.3 ± 0.6</td>
<td>11.6 ± 0.9***</td>
<td>15.8 ± 1.4***</td>
<td>18.3 ± 1.0***</td>
<td>9.0 ± 0.7</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>7.7 ± 0.8</td>
<td>10.0 ± 0.6</td>
<td>11.3 ± 1.0***</td>
<td>13.3 ± 1.0***</td>
<td>15.3 ± 1.2***</td>
<td>8.6 ± 0.8</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>3.4 ± 0.4</td>
<td>5.7 ± 0.5***</td>
<td>8.0 ± 0.7***</td>
<td>9.5 ± 0.9***</td>
<td>11.0 ± 1.0***</td>
<td>35 ± 0.6</td>
</tr>
<tr>
<td>Esophageal pressure (mm Hg)</td>
<td>4.2 ± 0.6</td>
<td>6.0 ± 0.7*</td>
<td>7.6 ± 0.6***</td>
<td>9.2 ± 0.8***</td>
<td>11.8 ± 0.7***</td>
<td>3.6 ± 0.7</td>
</tr>
<tr>
<td>PVR (dyn/sec/cm⁻⁵)</td>
<td>244 ± 42</td>
<td>255 ± 34</td>
<td>390 ± 22***</td>
<td>528 ± 84*</td>
<td>938 ± 93***</td>
<td>243 ± 31</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>88 ± 4</td>
<td>92 ± 3</td>
<td>85 ± 5</td>
<td>86 ± 6</td>
<td>74 ± 6*</td>
<td>82 ± 4*</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>34 ± 2</td>
<td>33 ± 1</td>
<td>37 ± 3*</td>
<td>39 ± 2**</td>
<td>44 ± 2***</td>
<td>37 ± 3</td>
</tr>
<tr>
<td>Qs/Qt (% C.O.)</td>
<td>14 ± 1</td>
<td>13 ± 2</td>
<td>15 ± 2</td>
<td>14 ± 1</td>
<td>21 ± 3</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>O₂ delivery (cc/min)</td>
<td>558 ± 29</td>
<td>526 ± 53</td>
<td>543 ± 16**</td>
<td>410 ± 18**</td>
<td>365 ± 11**</td>
<td>432 ± 48**</td>
</tr>
</tbody>
</table>

* Mean value ± SEM.
** Mean significantly different from mean at 0 PEEP (paired t test): * P < 0.05; ** P < 0.01; *** P < 0.001.

normal, but cardiac output remained below baseline (77% of control).

Arterial PO₂ decreased slightly at 20 cm PEEP, while PaCO₂ increased (Table 1). Intrapulmonary shunt did not change, but oxygen delivery decreased at each level of PEEP at which cardiac output decreased.

Acute Hypermovolemia

Rapid administration of Ringer’s lactate resulted in an increase in cardiac output from 3.0 (original baseline prior to first PEEP study) to 3.5 liters/min (P < 0.01). Central venous pressure increased modestly from 3.4 to 11.8 mm Hg, while wedge and left atrial pressure rose markedly to 23 mm Hg (Table 2). There was no change in esophageal pressure, and ventilation volume remained constant. Right atrial transmural filling pressure rose to 7 mm Hg, while left atrial transmural filling pressure rose to 18 mm Hg. This was accompanied by a decrease in PaO₂ from 88 to 67 mm Hg and an increase in shunt from 14 to 24%.

Increasing levels of PEEP caused the same degree of intrathoracic pressure rise as in normovolemia, suggesting no major compliance alteration (Fig. 2). Central venous pressure rose proportional to the rise in esophageal pressure, and there was no change in right atrial transmural filling pressure. Wedge and left atrial pressures, both very high after fluid administration, did not reflect the rising intrathoracic pressure, and both pressures fell slightly at low levels of PEEP. Left atrial transmural filling pressure decreased as PEEP increased and was 11 mm Hg at 15 and 20 cm PEEP (Fig. 4). Left atrial pressure remained equal to pulmonary wedge pressure at all levels of PEEP. Pulmonary vascular resistance remained normal through 15 cm PEEP and increased slightly at 20 cm PEEP when cardiac output fell (Fig. 5).

PaO₂ increased and intrapulmonary shunt decreased with increasing levels of PEEP, but, at 20 cm PEEP, oxygen delivery decreased due to a fall in cardiac output. After removal of PEEP, cardiac output did not rise, and intravascular pressures were all below baseline hypervolemic levels.

Chronic Fluid Overload

On the second day, all animals were grossly edematous and had gained 25 ± 2%
FIG. 1. Effect of PEEP in normovolemic baboons. As the level of PEEP increases, cardiac output falls. Intravascular pressures rise parallel to rising intrathoracic pressure. At 15 and 20 cm PEEP, wedge pressure rises higher than left atrial pressure.

body weight. Five of six survived and were studied 24 hr after fluid administration. The sixth animal extubated himself after 20 hr and died of airway obstruction prior to study. Cardiac output was lower, and wedge, left atrial, and central venous pressures were only slightly higher than on Day 1 prior to fluid administration (Table 3).

Tidal volume and minute ventilation were unchanged. The rise in intrathoracic pressure with increasing levels of PEEP was the same as in normovolemia and acute hypervolemia, suggesting no major change in compliance (Fig. 3). Intravascular pressures rose, reflecting the increased intrathoracic pressure, and there was no change in right or left atrial transmural filling pressures (Fig. 4). Left atrial pressure was 1 mm Hg higher than wedge pressure on Day 2, and PEEP was better tolerated than on Day 1 prior to fluid administration. Cardiac output did not fall until the animal was ventilated with 20 cm PEEP, as was the case in acute hypervolemia. No discrepancy developed between wedge and left atrial pressures (Fig. 2). Pulmonary vascular resistance rose at 20 cm PEEP at the time that cardiac output fell (Fig. 5).

The effect of PEEP on gas exchange and intrapulmonary shunt showed wide varia-
### TABLE 2

**EFFECT OF PEEP DURING ACUTE HYPERVOLUMIA WITH URETERAL LIGATION**

<table>
<thead>
<tr>
<th>Level of PEEP (cm H₂O)</th>
<th>C.O. (liters/min)</th>
<th>Mean BP (mm Hg)</th>
<th>Mean PA (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>Esophageal pressure (mm Hg)</th>
<th>PVR (dyn/sec/cm²)</th>
<th>PaO₂ (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>Qs/Qt (% C.O.)</th>
<th>O₂ delivery (cc/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.5 ± 0.2*</td>
<td>156 ± 7</td>
<td>33 ± 2</td>
<td>23.3 ± 1.0</td>
<td>23.2 ± 0.7</td>
<td>11.8 ± 1.0</td>
<td>4.6 ± 0.2</td>
<td>241 ± 32</td>
<td>67 ± 4</td>
<td>32 ± 2</td>
<td>24 ± 3</td>
<td>488 ± 36</td>
</tr>
<tr>
<td>5</td>
<td>3.4 ± 0.2</td>
<td>156 ± 6</td>
<td>30 ± 2*</td>
<td>21.5 ± 1.2*</td>
<td>21.0 ± 0.5*</td>
<td>11.1 ± 0.9</td>
<td>5.4 ± 0.2***</td>
<td>215 ± 23</td>
<td>70 ± 5</td>
<td>30 ± 1</td>
<td>24 ± 3</td>
<td>513 ± 43</td>
</tr>
<tr>
<td>10</td>
<td>3.4 ± 0.3</td>
<td>152 ± 5</td>
<td>29 ± 3*</td>
<td>21.3 ± 1.1*</td>
<td>20.8 ± 1.8</td>
<td>12.3 ± 1.0</td>
<td>6.4 ± 0.2***</td>
<td>219 ± 11</td>
<td>71 ± 5</td>
<td>30 ± 1</td>
<td>22 ± 3</td>
<td>525 ± 49</td>
</tr>
<tr>
<td>15</td>
<td>3.5 ± 0.1</td>
<td>162 ± 4</td>
<td>30 ± 2*</td>
<td>21.3 ± 1.1*</td>
<td>21.4 ± 1.4</td>
<td>15.3 ± 0.8*</td>
<td>8.6 ± 0.2***</td>
<td>220 ± 16</td>
<td>81 ± 4</td>
<td>32 ± 2</td>
<td>19 ± 3*</td>
<td>518 ± 24</td>
</tr>
<tr>
<td>20</td>
<td>3.0 ± 0.2a</td>
<td>158 ± 5</td>
<td>33 ± 2</td>
<td>24.0 ± 1.8</td>
<td>23.0 ± 1.4</td>
<td>16.8 ± 1.1**</td>
<td>10.6 ± 0.4***</td>
<td>286 ± 37*</td>
<td>87 ± 4</td>
<td>33 ± 2</td>
<td>17 ± 2*</td>
<td>450 ± 37</td>
</tr>
<tr>
<td>0</td>
<td>3.1 ± 0.2</td>
<td>162 ± 8</td>
<td>29 ± 2</td>
<td>19.6 ± 2.3</td>
<td>18.5 ± 1.9</td>
<td>11.0 ± 1.4</td>
<td>4.2 ± 0.4</td>
<td>272 ± 60</td>
<td>67 ± 6</td>
<td>32 ± 2</td>
<td>26 ± 4</td>
<td>454 ± 27</td>
</tr>
</tbody>
</table>

* Mean Value ± SEM.

a Mean significantly different from mean at 0 PEEP (paired t test): * P < 0.05; ** P < 0.01; *** P < 0.001.

Two groups, however, could be identified. Two animals had clinical pulmonary edema with large amounts of watery tracheal secretions. Both were severely hypoxic (PaO₂: 40 and 32 mm Hg), acidotic (pH 7.2) and had large intrapulmonary shunts (66 and 61%). They had the highest left atrial pressures after fluid loading on Day 1 (24 and 25 mm Hg) and had the highest left atrial pressures on Day 2 (13 and 14 mm Hg). Subsequent postmortem examination confirmed pulmonary edema with wet to dry lung ratios of 8.1:1 and 7.2:1. Both animals benefited greatly from PEEP, with marked reduction in intrapulmonary shunt (24 and 15% at 20 cm H₂O) and increase in PaO₂ (63 and 65 mm Hg). Cardiac output increased in one animal at 5, 10, and 15 cm PEEP and, in the other, at 5 and 10 cm PEEP. Oxygen delivery was improved at all levels of PEEP, but declined at 15 and 20 cm PEEP when cardiac output fell, despite a continued rise in PaO₂ and a fall in shunt (Fig. 6).

Three animals, despite equivalent fluid load and weight gain, had normal PaO₂, pH, and shunt. Wedge pressure equaled left atrial pressure, and both were lower than in the pulmonary edema group. No watery tracheal secretions were present and, at postmortem, no pulmonary edema was found (wet/dry lung weight ratio: 4.7:1, 4.6:1, and 4.3:1). These animals behaved like normovolemic animals with no change in shunt or PaO₂ with increasing PEEP. PEEP caused a greater fall in cardiac output than in the animals with pulmonary edema, and oxygen delivery diminished at output fell in all three animals. A 3-mm Hg discrepancy between wedge and left atrial pressures developed in the animal with the largest fall in cardiac output.

### Functional Hypovolemia

Cardiac output in upright animals with no PEEP was 1.8 liters/min, not statistically different from supine animals on Day 2. Central venous, wedge, and left atrial pressures were low (−3 to +3 mm Hg). Esophageal pressure demonstrated a rise in intrathoracic pressure similar to that seen in the previous experiments. Cardiac output, however, fell markedly with the application of PEEP, and only one animal was able to...
FIG. 2. Effect of PEEP in acute hypervolemia. Increasing intrathoracic pressure has little effect on high intravascular pressures, and cardiac output does not decrease until 20 cm PEEP. There is no discrepancy between wedge and left atrial pressure.

Four of five baboons died while on PEEP: two at 5 cm H$_2$O, one at 10 cm H$_2$O, and one at 20 cm H$_2$O. Insufficient data were collected for meaningful statistical analysis. Marked discrepancies, up to 6 mm Hg, between wedge and left atrial pressures developed in four of the five animals at the time of the greatest reduction in cardiac output. One animal survived the upright PEEP study, but had an 88% reduction in cardiac output at 20 cm PEEP.

DISCUSSION

When airway pressure is increased, intrathoracic pressure rises. This pressure is transmitted to intrathoracic vascular structures and may impair blood flow in the systemic veins [1, 7, 17], pulmonary circulation [5, 12], or myocardial circulation [8, 13]. Most striking in our normovolemic baboons was the marked rise in pulmonary vascular resistance at the time of fall in cardiac output and the development of a
discrepancy between wedge and left atrial pressures, suggesting obstruction to flow in the pulmonary vascular bed. Hobelmann et al. [5], using a similar protocol, studied baboons in the upright position and noted a greater fall in cardiac output, a larger wedge—left atrial pressure discrepancy, and a more marked rise in pulmonary vascular resistance at each level of PEEP than seen in our supine animals. Upright paralyzed animals are functionally hypovolemic due to dependent venous pooling, and the dangers of hypovolemia have been noted by others in patients [10] and animals [17]. Wedge pressure thus cannot be used as a reliable indicator of left atrial pressure and intravascular volume while using PEEP [5, 8, 12]. This is true despite apparent gross fluid overload as seen in our chronic hypovolemic animals on Day 2, when they were placed upright. Marked wedge—left atrial pressure discrepancy developed, and PEEP caused the death of four of the five animals.

These observations have been explained by viewing the pulmonary capillary as a Starling resistor in which flow across the pulmonary capillary bed is proportional to the difference between pulmonary artery pressure and pulmonary venous pressure (left atrial pressure), provided that pulmonary venous pressure is greater than alveolar pressure. When, however, alveolar pressure is greater than pulmonary venous pressure, flow is proportional to the difference between pulmonary artery pressure and alveolar pressure, and changes in pulmonary venous pressure have no influence on flow [11]. Thus, under circumstances of low left atrial pressures, as would be seen in hypovolemia, the pulmonary capillaries are compressed by PEEP, and the wedge pulmonary artery catheter reflects intra-alveolar pressure rather than left atrial pressure. Fluid infusion with elevation of left atrial pressure above intra-alveolar pressure overcomes the pulmonary vascular compression, equalizes wedge and left atrial pressures, and restores flow as shown in these experiments.

Fung and Sobin [2], using the sheet-flow concept, have postulated a progressive increase in pulmonary resistance as alveolar pressure increases relative to capillary hydrostatic pressure. The absolute cessation of flow postulated in the concept of

### TABLE 3

**EFFECT OF PEEP 24 HR AFTER FLUID ADMINISTRATION AND URETERAL LIGATION**

<table>
<thead>
<tr>
<th>Level of PEEP (cm H,O)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.O. (liters/min)</td>
<td>1.9 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>1.4 ± 0.2&lt;sup&gt;bb&lt;/sup&gt;</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>123 ± 7</td>
<td>119 ± 7</td>
<td>124 ± 8</td>
<td>119 ± 6</td>
<td>107 ± 7&lt;sup&gt;*&lt;/sup&gt;</td>
<td>114 ± 6</td>
</tr>
<tr>
<td>Mean PA (mm Hg)</td>
<td>20 ± 3</td>
<td>21 ± 2</td>
<td>20 ± 1</td>
<td>25 ± 2</td>
<td>29 ± 1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>9.6 ± 1.7</td>
<td>11.2 ± 0.6</td>
<td>11.0 ± 1.2</td>
<td>13.8 ± 0.6&lt;sup&gt;*&lt;/sup&gt;</td>
<td>17.0 ± 0.6&lt;sup&gt;*&lt;/sup&gt;</td>
<td>8.6 ± 1.1</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>10.6 ± 1.1</td>
<td>12.4 ± 0.9</td>
<td>11.8 ± 1.3</td>
<td>14.8 ± 0.5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>17.4 ± 0.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>9.2 ± 0.4</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>5.6 ± 0.8</td>
<td>8.0 ± 0.3&lt;sup&gt;*&lt;/sup&gt;</td>
<td>9.0 ± 0.4&lt;sup&gt;**&lt;/sup&gt;</td>
<td>11.8 ± 0.9&lt;sup&gt;***&lt;/sup&gt;</td>
<td>14.6 ± 0.5&lt;sup&gt;***&lt;/sup&gt;</td>
<td>4.4 ± 0.9</td>
</tr>
<tr>
<td>Esophageal pressure (mm Hg)</td>
<td>3.0 ± 0.8</td>
<td>4.7 ± 0.6&lt;sup&gt;**&lt;/sup&gt;</td>
<td>6.5 ± 1.0&lt;sup&gt;**&lt;/sup&gt;</td>
<td>7.2 ± 0.6&lt;sup&gt;***&lt;/sup&gt;</td>
<td>9.7 ± 0.9&lt;sup&gt;***&lt;/sup&gt;</td>
<td>2.2 ± 1.0</td>
</tr>
<tr>
<td>PVR (dyn/sec/cm&lt;sup&gt;5&lt;/sup&gt;)</td>
<td>419 ± 102</td>
<td>387 ± 71</td>
<td>488 ± 140</td>
<td>641 ± 97</td>
<td>870 ± 166&lt;sup&gt;∗&lt;/sup&gt;</td>
<td>383 ± 66</td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>61 ± 11</td>
<td>61 ± 8</td>
<td>71 ± 7</td>
<td>72 ± 5</td>
<td>73 ± 4</td>
<td>64 ± 9</td>
</tr>
<tr>
<td>PaCO&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>40 ± 5</td>
<td>39 ± 4</td>
<td>39 ± 4</td>
<td>38 ± 3</td>
<td>39 ± 2</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Qs/Qt (% C.O.)</td>
<td>34 ± 12</td>
<td>28 ± 7</td>
<td>19 ± 5</td>
<td>16 ± 4</td>
<td>13 ± 3</td>
<td>23 ± 8</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; delivery (cc/min)</td>
<td>273 ± 42</td>
<td>293 ± 50</td>
<td>317 ± 49</td>
<td>262 ± 44</td>
<td>221 ± 44</td>
<td>276 ± 42</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean value ± SEM.

<sup>b</sup> Means significantly different from mean at 0 PEEP (paired t test): * P < 0.05; ** P < 0.01; *** P < 0.001.
Starling's resistor would result in increased shunt, not in the progressive decrease seen in these animals. The sheet-flow concept explains the progressive increases in PVR (Fig. 5) seen in all animals as cardiac output falls. When left atrial and PAP are high in acute hypervolemia, pulmonary vascular resistance does not rise significantly until PEEP reaches high levels. One could postulate that the compression of the sheet is the controlling factor determining cardiac output.

Impaired right heart filling with positive pressure ventilation has been demonstrated [1, 7] and shown to be correctable by fluid administration [14]. We found no decrease in right or left heart filling pressure in normovolemic animals (Fig. 4) using esophageal pressure to determine transmural filling pressure. Harken and Giordano [3], using esophageal pressure, also found no change in transmural filling pressure with PEEP. On the other hand, Cournand et al. [1], Lenfant and Howell [7], and Qvist et al. [14] measured intrapleural pressure and noted a fall in transmural pressure. Both pleural and esophageal pressures are subject to inaccuracies in determining transmural

Fig. 3. Effect of PEEP in chronic hypervolemia. Intravascular pressures do not rise with increasing intravascular pressure until 15 cm PEEP, when cardiac output begins to fall.
pressures, and intrapericardial pressure should probably be measured for better determination of transmural filling pressure. It is likely that filling pressure of intra-thoracic veins is affected by rising intrathoracic pressure, just as the pulmonary vessels are, and further studies are in progress to determine the role of impairment of blood flow to the right heart.

Despite the maintenance of very high filling pressures in the acutely hypervolemic group, cardiac output decreased at 20 cm PEEP. Lozman et al. [8] found that left ventricular failure occurred in all patients as airway pressure was increased above 15 cm H2O and postulated interference with coronary blood flow. Powers and Dutton [13] have also demonstrated changes in ventricular function at high levels of PEEP and have implicated impaired myocardial blood flow at high levels of PEEP.

Harken et al. [4], on the other hand, have shown that, in postcardiac surgery patients, those with the highest left atrial pressures

![Diagram](image-url)

**Fig. 4.** Right and left atrial transmural filling pressures with PEEP. In normovolemia there is no change in filling pressure as cardiac output falls with increasing PEEP. In hypervolemia, cardiac output is maintained, and high left atrial transmural pressure decreases. In chronic hypervolemia, there is no change in transmural filling pressure.
not only did not decrease their cardiac output with PEEP, but frequently increased their cardiac output at low levels of PEEP. He felt that in conditions where left ventricular function limits cardiac output, an increase in intrathoracic pressure, relative to peripheral resistance, caused by PEEP could be expected to increase cardiac output. Our baboons with severe chronic fluid overload and pulmonary edema on Day 2 had the highest left atrial pressure and benefited from PEEP with an improvement in cardiac output with low levels of PEEP. Similarly, Sykes et al. [17] noted no change in cardiac output in animals in gross congestive heart failure placed on PEEP, whereas, normovolemic animals sustained a fall in cardiac output. The decrease in left atrial transmural filling pressure seen in the acute hypervolemic animals may be related to improved ventricular function at low levels of PEEP and may explain the maintenance of cardiac output.

Qvist et al. felt that changes in cardiac output were related solely to changes in filling pressure and that no circulatory adaptation occurred, even after 8 hr of ventilation with PEEP [14]. Blood trans-
fusion corrected the filling deficit and improved cardiac output. However, when PEEP was removed, he noted an acute rise in cardiac index which remained high due to persistently elevated transmural filling pressures. Rebound hypervolemia was notably absent in our fluid-loaded baboons, and cardiac output rarely returned to baseline level on removal of PEEP. We administered crystalloid solution rather than blood and used higher levels of PEEP. Qvist et al. [14] used only 12 cm H₂O PEEP and may have avoided the myocardial impairment at higher pressures.

Sykes et al. [17] postulated that reduced lung compliance accompanying hypervolemia might cause a decrease in the proportion of airway pressure transmitted to the intrapleural space and, thus, might protect from cardiac output depression. In these experiments tidal volume remained constant, and acute or chronic hypervolemia did not cause significant alteration in the transmitted intrathoracic pressure as determined by esophageal pressure. Elevation of intravascular pressure above transmitted intrathoracic pressure was of greatest importance in protecting from cardiac output depression. Alterations in the level of PEEP may cause changes in compliance, and determination of maximum compliance may be a clinically useful means of determining the optimum PEEP level clinically when cardiac output measurement is not available [15].

Cardiac output is an important parameter

![Graph](image-url)

Fig. 6. Effect of PEEP in baboons with pulmonary edema. Despite continuing rise in PaO₂ and fall in shunt, oxygen delivery decreases at 15 and 20 cm PEEP as cardiac output falls.
in patients ventilated with high levels of PEEP. Despite an increase in arterial oxygen, a decrease in cardiac output may result in decreased oxygen delivery with a net deleterious effect. Powers et al. [12] found an almost linear relation between cardiac output and tissue oxygen consumption. In one-third of the instances in their series, the observed fall in output outweighed the improved arterial oxygen content with a consequent decrease in oxygen delivery and tissue oxygen consumption. In our series, a decrease in cardiac output was closely related to a decrease in oxygen delivery in all conditions (normovolemia, \( r = 0.83 \); acute hypervolemia, \( r = 0.92 \); chronic hypervolemia, \( r = 0.79 \)), indicating the importance of knowing the effect of PEEP on cardiac output. Oxygen delivery decreased as cardiac output decreased, despite a continuing rise in \( \text{PaO}_2 \) and a decrease in shunt (Fig. 6).

The usual monitors of intravascular volume (wedge pressure and central venous pressure) may be unreliable as indices of adequate intravascular volume since they rise with increasing intrathoracic pressure. A sudden increase in wedge pressure with an increase in airway pressure should alert one to the possibility that measured wedge pressure may not be an accurate reflection of left atrial pressure and that cardiac output may be falling. Fluid administration may correct cardiac output depression with PEEP and may permit ventilation with higher levels of PEEP without deleterious effects.

**SUMMARY**

The effects of increasing levels of PEEP were studied in six baboons under conditions of normovolemia, acute hypervolemia, chronic hypervolemia, and functional hypovolemia. In normovolemic animals, PEEP caused a significant fall in cardiac output with a marked increase in pulmonary vascular resistance and the development of a discrepancy between wedge and left atrial pressures. Acute fluid loading prevented the wedge–left atrial pressure discrepancy, the rise in pulmonary vascular resistance, and the fall in cardiac output. Chronically hypervolemic animals were less susceptible to cardiac output depression than were normovolemic animals. Those with pulmonary edema benefited greatly from PEEP, while those with normal lungs derived no benefit. Hypovolemic animals sustained profound falls in cardiac output with PEEP.

**REFERENCES**


