Effects of Positive End-expiratory Pressure on Gas Exchange in Dogs with Normal and Edematous Lungs

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The effects of positive end-expiratory pressure (PEEP) at 5, 10, 15, and 20 cm H₂O on the distribution of ventilation–perfusion (Vₐ/Q) ratios was determined in four normal dogs and in ten with oleic acid–induced acute hemorrhagic pulmonary edema. Tidal volume and frequency were held constant at all times with mechanical ventilation during intravenous pentobarbital and gallamine anesthesia. Normal dogs had little or no shunt, and no areas of low (<0.1) or high Vₐ/Q (>10.0) at zero end-expiratory pressure (intermittent positive-pressure breathing). In these animals increasing PEEP caused progressive depression of cardiac output, associated with an increase in ventilation to both high Vₐ/Q and unperfused regions. PEEP > 10 cm H₂O resulted in a reduction in PaₐO, and an increase in PaₐCO₂. In dogs with pulmonary edema, PEEPs of 5 and 10 cm H₂O resulted in dramatic reductions in shunt, virtual obliteration of low Vₐ/Q regions, and marked improvement in PaₐO₂. However, at 15 and 20 cm H₂O PEEPs, high Vₐ/Q and dead space ventilation with CO₂ retention again developed in all but the most severely affected (shunt > 40 per cent) dogs. (Key words: Ventilation, perfusion; Ventilation, positive end-expiratory pressure; Lung, ventilation–perfusion ratio.)

In certain patients with acute respiratory failure, positive end-expiratory pressure (PEEP) breathing clearly produces marked improvement in pulmonary gas exchange. However, in other patients, PEEP produces equivocal and even detrimental changes in gas exchange, often combined with considerable reductions in cardiac output. In order to understand the reason for these conflicting responses it would be useful to know the effects of PEEP on the distribution of ventilation–perfusion ratios. This can be done with a new method based on the steady-state elimination of six intravenously infused inert gases, recently described by Wagner et al. This technique gives an essentially continuous distribution of ventilation–perfusion (Vₐ/Q) ratios over the Vₐ/Q range 0.005 to 100, as well as shunt (Vₐ/Q = 0) and dead space, defined here as Vₐ/Q > 100. Accordingly, this method was employed to assess the effects of four levels of PEEP (5, 10, 15, and 20 cm H₂O) on the distributions of Vₐ/Q ratios in normal dogs and in dogs with moderate to severe acute hemorrhagic pulmonary edema induced by oleic acid injection.

Methods

Fourteen mongrel dogs weighing 18–31 kg were anesthetized with pentobarbital (25 mg/kg, iv). The trachea was intubated with a cuffed endotracheal tube, and the dog was restrained in the supine position. Constant minute ventilation was maintained with a Harvard respirator at constant tidal volumes of 12–15 ml/kg, with the frequency adjusted to produce Paco₂ 30–35 torr during intermittent positive-pressure breathing (IPPB) prior to oleic acid injection. Spontaneous respiratory efforts were prevented with 20–40 mg gallamine, iv, from time to time, as well as further small doses of pentobarbital, administered intravenously as needed. Catheters were placed into the femoral vein, main pulmonary artery (Swan-Ganz) and femoral artery.

In ten dogs, acute hemorrhagic pulmonary edema was produced with 0.06 to 0.15 ml/kg oleic acid injected into the right ventricle. Four dogs served as normal controls and received no oleic acid.

A solution of six inert gases was prepared as described previously and infused at 2.5 ml/min intravenously. During steady-state conditions (stable arterial blood and end-tidal Pao₂ and PCO₂ values and vascular pressures) and after infusion for at least 30 minutes, we measured: 1) inert gas concentrations in mixed venous and arterial blood and mixed expired gas using a Beckman GC 72–5 gas chromatograph, as previously described; 2) Pao₂, Paco₂ and pH in arterial and mixed venous blood, and Pao₂ and Paco₂ in mixed expired gas, using Radiometer blood-gas electrodes; 3) cardiac output, using indocyanine green dye and a Gilford densitometer; 4) systemic and pulmonary arterial pressures and mean airway pressure, with Statham P23 Db pressure transducers; 5) minute ventilation with a calibrated Wright's respirometer; 6) anatomic dead space by means of the Fowler method, using the expired CO₂ tracing. Expired CO₂ concentration was measured continuously with a Varian M3 mass spectrometer and expired volume with an Ohio 800 spirometer. A six-channel Brush recorder was used to log inspired and expired oxygen and carbon dioxide partial pressures, expired volume,
Fig. 1. Results in a normal dog. Retention – solubility (arterial)/
(venous) and excretion – solubility (expired)/(venous) curves
on the left match the derived distributions of ventilation–perfu-
sion ratios on the right, during a) IPPB or zero end-expiratory
pressure, b) 5 cm H₂O PEEP, c) 10 cm H₂O PEEP, d) 15 cm
H₂O PEEP, e) 20 cm H₂O PEEP. Broken lines on the left
represent the measured retention – solubility and excretion
– solubility curves, the associated solid lines represent homo-
genous lungs with shunt and dead space. Note that as PEEP was
increased, increasing amounts of ventilation were seen in units
with high ventilation–perfusion ratios.

Fig. 2. Example of moderate pulmonary edema. Retention
– solubility and excretion – solubility curves match derived dis-
tributions of ventilation–perfusion ratios during a) IPPB, b)
5 cm H₂O PEEP, c) 10 cm H₂O PEEP, d) 15 cm H₂O PEEP, e)
20 cm H₂O PEEP.
indocyanine green dye concentration, and mean airway and vascular pressure data. In addition, the $P_{50}$ of the blood was measured with a Co-Oximeter (Instrumentation Laboratories, Lexington, Mass.). Following the control study at zero end-expiratory pressure (1PPB), studies were made during 5, 10, 15 and 20 cm H₂O PEEP in random sequence with repeat 1PPB control studies separating successive levels of PEEP. A low-inertia magnetic valve (Special Surgical Instrument Co., San Diego, Cal.) was used to produce positive end-expiratory pressure. All but four dogs (those with the most severe pulmonary edema, which needed 100 per cent oxygen) were studied while breathing room air, but in each dog inspired $O_2$ concentration was held constant throughout the study.

**Computations**

Measured values of mixed arterial-to-mixed venous blood concentration ratio (retention, $R$) and mixed expired-to-mixed venous blood concentration ratio (excretion, $E$) for each inert gas were plotted against its measured solubility. These plots were then analyzed by digital computer (CDC 3600), which yielded distributions of both blood flow and ventilation with respect to $V_{\text{a}}/Q$, as well as shunt and dead space. It should be kept in mind that other distributions are compatible with the measured inert gas data. We have developed a method for evaluating the variability of distributions associated with a particular set of retentions and applied it to several of the data sets in this study. The range of allowable distributions around the representative distributions reproduced here is sufficiently small that the physiologic implications are unaltered. In particular, the bimodal character of the distributions seen during ventilation by PEEP is well established, in that it was not possible to fit the data with unimodal curves. The computer was also used to calculate $P_{\text{O}_2}$ and $P_{\text{CO}_2}$ values of arterial blood and mixed expired gas corresponding to these distributions, incorporating the measured values of mixed venous blood $P_{\text{O}_2}$ and $P_{\text{CO}_2}$, $P_{50}$, hemoglobin, hematocrit, temperature, and acid-base status.

Cardiac output was calculated by planimetry of the indocyanine green dye concentration curves.

**Results**

**Distributions of Ventilation–Perfusion Ratios**

**Normal dogs.** These dogs showed narrow distributions of ventilation and blood flow during intermittent positive-pressure breathing (end-expiratory pressure zero). An example of the results in one dog is shown in figure 1. In this group of animals there was virtually no blood flow or ventilation to regions with very low $V_{\text{a}}/Q$ (<0.1) or high $V_{\text{a}}/Q$ (>10.0). There was generally little or no shunt (mean 1.6 per cent ± 0.04 SD), the shunt of 7.2 per cent in figure 1 being exceptionally high. Dead space ventilation, which includes anatomic dead space, regions with $V_{\text{a}}/Q$ ratios > 100.0, and instrumented dead space (70 ml), was 36 per cent of minute ventilation (mean for four normal dogs).

Figure 1 also shows an example of the results of progressively increasing PEEP in normal dogs. Any
shunt that was present was gradually reduced as the pressure was increased (figures 1 and 6). However, this limited improvement in the distribution was accompanied by a progressive reduction in cardiac output and the development of high \( V_{A}/Q \) regions, which occurred typically when PEEP exceeded 10 cm H\(_2\)O (fig. 4). Therefore, the total amounts of both ventilation and blood flow to lung units with \( V_{A}/Q \) ratios in the "normal" range (0.1 < \( V_{A}/Q < 10.0 \)) diminished progressively with PEEP. In the example shown in figure 1, the amounts of ventilation and blood flow present within this normal range were 4.3 l/min and 3.8 l/min, respectively for 5 cm H\(_2\)O PEEP, and the values were reduced to 1.7 l/min for both when PEEP was increased to 20 cm H\(_2\)O. Dead space ventilation, on the other hand, showed an almost linear increase with end-expiratory pressure (fig. 8).

No area of low or zero \( V_{A}/Q \) was created by high PEEP (figs. 1, 2, 3, and 6).

Dogs with moderate pulmonary edema. These were identified for convenience as those dogs having less than 40 per cent shunt during IPPB (fig. 6). In these dogs there was blood flow in three distinct regions of the \( V_{A}/Q \) spectrum during IPPB (fig. 2): 1) regions with \( V_{A}/Q < 0.005 \) (shunt); 2) regions with \( V_{A}/Q \) between 0.005 and 0.1 (very low \( V_{A}/Q \)); 3) regions within the "normal" range of \( V_{A}/Q \) ratios (0.1 < \( V_{A}/Q < 10.0 \)). The latter were shifted toward slightly higher \( V_{A}/Q \) ratios (mean \( V_{A}/Q = 1.63 \)) than in normal dogs due to their reduced blood flow.

Dramatic reductions in shunt occurred with 5 and 10 cm H\(_2\)O PEEP (as described previously),\(^{10,16}\) and in most cases complete obliteration of very low \( V_{A}/Q \) regions also occurred even at 5 cm H\(_2\)O PEEP (though not in the example shown in fig. 2). However, at the

![Graph 1: Ventilation (top) and Blood Flow (bottom) vs. End Expiratory Pressure (cm H\(_2\)O)]

**Table 1. Effects of 5-cm H\(_2\)O increments of PEEP in Three Examples of Moderate (Dog 7) and Severe (Dogs 8 and 14) Acute Hemorrhagic Pulmonary Edema, on Pulmonary Gas Exchange and \( V_{A}/Q \) Distribution**

<table>
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<th></th>
<th>PEEP (cm H(_2)O)</th>
<th>( V_{A}/Q )</th>
<th>Per Cent Shunt</th>
<th>( Q_{BL} )</th>
<th>( V_{A} )</th>
<th>Per Cent ( V_{A}/Q )</th>
<th>( F_{\text{A,O}} ) (mm Hg)</th>
<th>( F_{\text{A,N}} ) (mm Hg)</th>
<th>( V_{A}/Q )</th>
<th>( Q_{A},# )</th>
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<td>427</td>
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<td>44</td>
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* Inert-gas method.
† Mean \( V_{A}/Q \) of the distribution of blood flow.
‡ Standard deviation of the distribution of blood flow.
§ Mean \( V_{A}/Q \) of the distribution of ventilation.
¶ Standard deviation of the distribution of ventilation.
same time, total pulmonary blood flow was reduced as PEEP was increased. As a result, blood flow to well-ventilated regions of the lung, calculated from the product of total pulmonary blood flow (Qp) and the factor (1.0 - fractional shunt), remained essentially unchanged as PEEP was increased (fig. 7). This is in strong contrast to the same index of what might be termed non-shunt pulmonary blood flow calculated for normal dogs (fig. 7). Here, since there was virtually no shunt at any PEEP, total and therefore non-shunt pulmonary blood flow decreased progressively.

Major changes also occurred in the distribution of ventilation. Since tidal volume and frequency were held constant, no change in total ventilation occurred with increasing PEEP. However, non-dead space ventilation decreased progressively as PEEP was increased due to an increase in unperfused lung (dead space, fig. 8). Independent measurement of anatomic dead space by the Fowler method (fig. 8) suggests that this increase in dead space is due entirely to an increase in conducting airway caliber resulting from the increase in lung volume caused by PEEP.

In addition, at the higher levels of PEEP, high $V_a/Q$ regions developed (fig. 2). These received large proportions of the total ventilation and, as a result, ventilation in the well-perfused regions was reduced by large amounts. Because of this, the mean position of the perfusion distribution ($VQ_r$, table 1, Dog 7)

![Fig. 5. Dispersion (mean standard deviation of the distribution of $V_a/Q$ ratios for normal (— ● —) and pulmonary-edema (— ○ —) dogs at 0, 5, 10, 15, and 20 cm H$_2$O end-expiratory pressure, for the distribution of a) ventilation, and b) blood flow.](image)

![Fig. 6. Upper panel: responses of intrapulmonary shunts ($V_a/Q$ < 0.005) in normal (— ● —) and pulmonary-edema (— ○ —) dogs to 5, 10, 15, and 20 cm H$_2$O PEEP, in comparison with the mean value at IPPB. Lower panel: normalized responses of shunts to 5, 10, 15, and 20 cm H$_2$O PEEP in comparison with IPPB (100 per cent or control value). The bars represent the mean normalized shunt value for the normal (no oleic acid) dogs (left bar), and the mean normalized shunt for pulmonary-edema dogs (right bar) at 5, 10, 15, and 20 cm H$_2$O PEEP.](image)

often shifted to the left, and that of ventilation to the right. CO$_2$ retention was often observed under these conditions.

Dogs with severe pulmonary edema. These were defined as having shunt greater than 40 per cent during IPPB (fig. 6). An example is shown in figure 3. As positive end-expiratory pressure was applied, shunt again diminished dramatically, thus increasing non-shunt blood flow (as previously defined) to well-ventilated units in spite of the progressive reduction in cardiac output (for example, Dog 8, table 1). Furthermore, high $V_a/Q$ regions did not develop until PEEP reached 15 cm H$_2$O, a level generally
higher than in the less severely affected dogs. Consequently, compared with these dogs, CO₂ retention with increasing PEEP was much less marked (table 1, Dogs 8 and 14). Lungs with severe pulmonary edema also showed a considerable leftward shift of the perfusion distribution from "high normal" V'A/Q ratios toward 1.0 with increasing PEEP, reflecting the reduction of shunt and consequent increase in non-shunt blood flow. For example, in figure 3 the mean V'A/Q ratio of the entire blood flow distribution decreased from 4.07 (IPPB) to 3.11 (20 cm H₂O PEEP). The ventilation distribution also shifted to the left (table 1, Dogs 8 and 14). This tendency of the ventilation distribution to shift to lower V'A/Q ratios in dogs with severe pulmonary edema is in contrast to the progressive increases seen in both normal and moderately affected dogs at all levels of PEEP, discussed above. This difference can be attributed to the less marked development of high V'A/Q regions with PEEP in the severely affected dogs.

The degrees of dispersion (log standard deviation) of the distributions of ventilation were similar for normal dogs and both groups of dogs with pulmonary edema during IPPB. They showed progressive increases with PEEP in all groups, due to the appearance of high V'A/Q areas. The dispersion of the distribution of blood flow in normal dogs showed little change even at higher PEEP because of the minimal blood flow to both low and high V'A/Q regions at any level. Dogs with pulmonary edema, on the other hand, showed significant reductions in dispersion of blood flow with as much as 10 cm H₂O PEEP (table 1). At 10 cm H₂O PEEP the degree of dispersion reached the normal range (fig. 5). This was primarily due to the disappearance of low V'A/Q regions, and a slight narrowing of the main body of the distribution of blood flow.

**Blood Gases**

In normal dogs the combined effects of reduced non-dead space ventilation and reduced non-shunt blood flow (due to reduced cardiac output, with its consequent reduction in mixed venous oxygen concentration) led to a significant reduction in PaO₂ from a mean of 75.4 ± 7.0 (SD) torr during IPPB to 66.5 ± 5.5 torr at 20 cm H₂O PEEP. Similarly, carbon dioxide excretion was impaired, leading to an increase in PaCO₂ from 30.4 ± 3.3 torr during IPPB to 42.7 ± torr at 20 cm H₂O PEEP (at constant tidal volume and frequency).

Dogs that had pulmonary edema, however, showed improved arterial oxygenation as the shunt and low V'A/Q regions were either reduced or abolished. Carbon dioxide retention did not appear in dogs that had moderate pulmonary edema unless at least 10 cm H₂O PEEP was applied. This corresponded to the appearance of a mode of very high V'A/Q units. Dogs that had severe pulmonary edema, however, showed reductions in PaCO₂ at all PEEP levels, compared with IPPB, due to progressive increases in non-shunt blood flow.

These changes in arterial blood-gas tensions were well predicted from the derived V'A/Q distributions (correlation coefficient between measured and predicted PaO₂ was 0.91, and the relationship not different from one of identity). The progressive disparity at higher PaO₂'s (>100 torr), as shown in

![Image](https://anesthesiology.pubs.asahq.org)
figure 9, has been discussed previously.\textsuperscript{7} It can be explained in part by the inaccuracy of blood-gas electrodes at high blood oxygen tensions and in part by the presence of bronchial and thebesian shunts, which are not detected by the inert gas method, but which do lower Pa\textsubscript{O\textsubscript{2}} during breathing of 100 per cent O\textsubscript{2}.

**Discussion**

**RELATIONSHIPS BETWEEN ARTERIAL BLOOD P\textsubscript{O\textsubscript{2}} AND P\textsubscript{CO\textsubscript{2}}, CARDIAC OUTPUT AND VENTILATION, AND DISTRIBUTION OF VENTILATION–PERFUSION RATIOS**

This study confirms the well-known observations that application of positive end-expiratory pressure can produce dramatic improvement in pulmonary gas exchange in pulmonary edema, but also can result in impairment of gas exchange, particularly for CO\textsubscript{2}. The multiple-inert-gas method clarifies the mechanisms involved because it gives information about the shape, position and dispersion of the distributions of ventilation–perfusion ratios.

**Normal Dogs**

Progressive increases in PEEP increased end-expiratory lung volume and, presumably by increasing traction on the airways, increased anatomic dead space as measured by the Fowler method. The dead space given by the inert-gas method, which includes both the above-mentioned anatomic dead space and that due to any completely unperfused alveoli, was found to agree well with that obtained with the Fowler method, suggesting that PEEP did not deprive alveoli of their blood flow completely. However, as much as half of the alveolar ventilation was found to be "wasted" in lung units having very high ventilation–perfusion ratios (very little blood flow). Presumably, PEEP caused redistribution of blood flow away from units that remained ventilated, but the anatomic basis of this redistribution is not apparent. By contrast, PEEP was never observed to give rise to areas of low or zero V\textsubscript{A}/Q, but the well-known depression of cardiac output with increase in PEEP\textsuperscript{16} was found in the present studies. The net effects of these changes in the amounts and patterns of distribution of ventilation and blood flow are relatively straightforward. The reduced cardiac output resulted in a lower venous blood P\textsubscript{O\textsubscript{2}} and higher venous blood P\textsubscript{CO\textsubscript{2}}, but in the absence of areas of low V\textsubscript{A}/Q, on the other hand, explains the reduction in P\textsubscript{a\textsubscript{O\textsubscript{2}}}, and increase in P\textsubscript{a\textsubscript{CO\textsubscript{2}}} (of approximately equivalent amounts) and was probably responsible for most of the impairment of gas exchange that was observed.\textsuperscript{16}

**Dogs with Moderate Edema (Shunts Less than 40 per cent)**

The increase in anatomic dead space and the development of high V\textsubscript{A}/Q areas with PEEP occurred as in normal dogs, and at constant tidal volume and frequency accounted for the rightward shift and increased dispersion of the distribution of ventilation. In addition, increasing PEEP progressively reduced the shunt and also abolished the regions of low V\textsubscript{A}/Q. This lessened the dispersion of the perfusion distribution and made more of the cardiac output available for gas exchange. However, at the same time, blood flow remained approximately constant (table 1, Dog 7). Because non-dead space ventilation decreased with PEEP while non-shunt blood flow did not, the perfusion distribution shifted to the left so that its mean V\textsubscript{A}/Q (table 1, Dog 7) decreased. The constancy of non-shunt blood flow accounts for the observed lack of reduction of venous blood P\textsubscript{O\textsubscript{2}} with PEEP in this group, as opposed to normal animals. The reduction in perfusion of low or zero V\textsubscript{A}/Q areas overrode the deleterious effect of the leftward shift of the perfusion distribution and explained the increase in P\textsubscript{a\textsubscript{O\textsubscript{2}}} with PEEP. The progressive decrease in alveolar ventilation, with increasing amounts of alveolar ventilation being "wasted" on areas of high V\textsubscript{A}/Q, explains the CO\textsubscript{2} retention, as for the normal dogs.

**Dogs with Severe Edema (Shunts Greater than 40 per cent)**

Once again, anatomic dead space increased with PEEP, but the appearance of high V\textsubscript{A}/Q areas was
much less marked at any level of PEEP than in either normal or moderately affected dogs. Thus, ventilation distributions did not develop as much dispersion as in the normal or moderately affected animals (Table 1).

The addition of non-shunt blood flow brought about by the dramatic reductions in shunt in shunt more than compensated for the reduction in cardiac output (Table 1) caused by PEEP, so that net absolute blood flow to ventilated lung units actually increased compared to normal dogs where it decreased, and moderately affected dogs where it remained constant. This increase in non-shunt blood flow, together with the much less marked appearance of high V A/Q areas, actually resulted in a net leftward shift of the distributions of both blood flow and ventilation (Table 1) in severely affected dogs. The lesser development of high V A/Q areas, together with the reduction in shunt, resulted in a decrease in PaO 2 (Table 1). The dramatic reductions in shunt were clearly responsible for the increase in PaO 2 in the severely affected dogs.

Thus, the changes in PaO 2 with increases in PEEP, which take opposite directions in moderately and severely affected animals, can be explained rationally with the use of the inert-gas approach. This study demonstrates the complexity of interacting physiologic changes that are brought about by the application of positive end-expiratory pressure in dogs.

THE PATTERN OF VENTILATION–PERFUSION INEQUALITY RESULTING FROM APPLICATION OF PEEP

A highly reproducible result at high levels of PEEP was the development of bimodal distributions of ventilation. Numerical analysis has confirmed that, allowing for experimental error, the data are not compatible with distributions of fewer than two modes. The results imply that perfusion is either grossly reduced by PEEP (high V A/Q mode) or hardly affected at all (normal V A/Q mode). Injection of microspheres shows that the regions of lung whose perfusion is grossly reduced are the uppermost areas, implying that gravitational factors are important.

Direct observation suggests that in these areas the capillaries are closed, but the vessels in the corners of the alveolar walls continue to be perfused, albeit at a grossly reduced rate. §§ However, further investigation will have to be done in order to explain the bimodality of the distributions. Whatever the mechanism responsible for the high V A/Q areas, their development probably explains much of the increase in physiologic dead space previously observed under conditions of positive end-expiratory pressure ventilation. 16,18

References


§ Wagner WW: Personal communication.