Positive End-Expiratory Pressure (PEEP); Indications and Physiologic Considerations

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Chest 1972;62;86S-94S

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Positive end-expiratory pressure ventilation has recently been reintroduced into the practice of clinical medicine. The purpose of this article is to present our experience with this form of therapy, to review the current literature, and to explore the theoretic basis for its use.

HISTORICAL BACKGROUND

In 1967, Ashbaugh and Petty revived the use of continuous positive end-expiratory pressure ventilation (PEEP) for the treatment of the acute respiratory distress syndrome in adults (ARDS). This method was first introduced in 1938 for the treatment of acute pulmonary edema secondary to congestive heart failure, but had been abandoned in recent years due to the development of potent diuretics and rapid acting digitalis preparations. PEEP was further studied in the early 1940’s as a means of increasing the partial pressure of alveolar oxygen when ambient pressures were low, to enable pilots to fly at high altitudes. Because of the discomfort of the spontaneously breathing pilot and impairment of venous return and cardiac output, intermittent positive pressure breathing (IPPB) was introduced and essentially replaced PEEP in aviation.

Since the initial case reports by Ashbaugh and Petty, a number of investigators have confirmed the value of PEEP in the treatment of the acute adult respiratory distress syndrome. It has been variously known as CPPB (continuous positive pressure breathing), PEPP (positive expiratory pressure plateau), and CPPV (continuous positive pressure ventilation). In 1971, Gregory et al showed remarkable improvements in arterial oxygen tension (PaO₂) in the idiopathic respiratory distress syndrome of the newborn, utilizing CPAP (continuous positive airway pressure).

TECHNIQUE

In the patients we have treated, only volume-cycled ventilators (Emerson or Bennett MA-1) were used. The patients were not permitted to assist the ventilator, and hence, many needed heavy sedation and one patient was kept continuously paralyzed with intravenous curare. PEEP was instituted by inserting the expiratory line under 5, 10 or 15 cm H₂O. Several volume-cycled ventilators have PEEP devices built in or attachments available; however, these are usually expensive compared to the water seal. It should be noted that expiratory retard, which is available on many IPPB machines, is not the same as PEEP. In treating newborns with the idiopathic respiratory distress syndrome, Gregory et al permitted spontaneous breathing only, with either endotracheal intubation, bag and a 30 cm under-water “pop-off” safety valve or, what would appear preferable, a plastic continuous pressure head chamber which eliminates the need for tracheal intubation (Fig 1).

PEEP: CLINICAL STUDIES

Eight patients were studied by us, and their diagnoses and initial blood gas determinations are presented in Table 1. In spite of a markedly

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INDICATIONS AND PHYSIOLOGIC CONSIDERATIONS OF PEEP

Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Primary Diagnosis</th>
<th>Pulmonary Diagnosis</th>
<th>Outcome</th>
<th>Cause of Death</th>
<th>Initial Arterial Blood Gas</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FL02</td>
</tr>
<tr>
<td>1</td>
<td>Peritonitis</td>
<td>Diffuse consolidation</td>
<td>Died</td>
<td>Respiratory failure</td>
<td>0.94</td>
</tr>
<tr>
<td>2</td>
<td>Peritonitis, acute tubular necrosis</td>
<td>Diffuse interstitial edema + diffuse consolidation</td>
<td>Died</td>
<td>Septicemic shock</td>
<td>0.80</td>
</tr>
<tr>
<td>3</td>
<td>Post-necrotic cirrhosis, hepatoma, liver transplant, hepatorenal syndrome, hyperdynamic shock, massive transfusion</td>
<td>Diffuse interstitial edema + diffuse consolidation</td>
<td>Died</td>
<td>Hyperdynamic shock</td>
<td>0.60</td>
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<tr>
<td>4</td>
<td>Carcinoma pancreas, whipple resection, massive transfusion, septicemic shock</td>
<td>Diffuse interstitial edema + diffuse consolidation</td>
<td>Died</td>
<td>Septicemic shock</td>
<td>0.96</td>
</tr>
<tr>
<td>5</td>
<td>Carcinoma larynx, laryngectomy, aspiration pneumonia, septicemic shock</td>
<td>Diffuse consolidation</td>
<td>Died</td>
<td>Septicemic shock</td>
<td>0.96</td>
</tr>
<tr>
<td>6</td>
<td>Septicemic (?) shock, diabetes mellitus</td>
<td>Diffuse interstitial edema</td>
<td>Lived</td>
<td>—</td>
<td>0.98</td>
</tr>
<tr>
<td>7</td>
<td>Septicemic shock, acute tubular necrosis, disseminated intravascular coagulation</td>
<td>Diffuse interstitial edema</td>
<td>Lived</td>
<td>—</td>
<td>0.84</td>
</tr>
<tr>
<td>8</td>
<td>Resection, dissecting thoracic aneurysm, cardiopulmonary bypass</td>
<td>Diffuse interstitial edema</td>
<td>Lived</td>
<td>—</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Elevated (A-a)O₂ gradient, the PaCO₂ was appropriate in all but one patient (case 8) who had not adequately compensated for his existing metabolic acidosis.

As in the other studies, the PaO₂ rose and the (A-a)O₂ gradient fell in each of the eight patients treated with PEEP (Fig 2 and 3). In general, a stepwise increase in PaO₂ was associated with a stepwise (5, 10 and 15 cm H₂O) increase in the level of PEEP. The magnitude of response, however, varied considerably among patients, and one patient did not have a rise in PaO₂ until 15 cm H₂O PEEP was reached. Of the eight patients, three were successfully treated with PEEP and weaned from the respirator (Table 1). The major pulmonary pathology in these patients, based on interpretation of their chest x-ray films, was interstitial pulmonary edema. Of the five patients who succumbed, four died from progressive and irreversible shock and one died (Case 1) from irreversible pulmonary insufficiency. Although this patient responded to PEEP, the response was not sufficient to lower the FIO₂ below 0.8. The chest x-ray film in this patient and Case 5 revealed diffuse consolidation. A mixture of consolidation and alveolar infiltration was seen in Cases 2, 3 and 4.

The data of Gregory et al in treating the idiopathic respiratory distress syndrome of the

Figure 2. Elevations in arterial oxygen tension (PaO₂) with graded increases in positive end-expiratory pressure (PEEP). Although each patient responded to some degree, the magnitude of response varied greatly among patients. (Reprinted with permission of the Journal of Trauma.)
newborn is quite similar to the data in adults, and shows a stepwise increase in PaO_2 with increasing levels of PEEP and a variability in magnitude of response among the babies treated (Fig 4).

The rapidity of rise and fall in PaO_2 with PEEP on and off was shown in the study by Kumar et al. With PEEP, the PaO_2 increases immediately, approaching the early maximum within 15 to 25 minutes. Similarly, the effectiveness of PEEP is also rapidly lost when it is discontinued. We found a similar immediate rapid response to PEEP, but in addition, noted a progressive slow improvement in PaO_2 over 12 to 48 hours (Fig 6). The chest roentgenogram usually improved during this time also, although the improvement in PaO_2 always preceded improvement in the x-ray picture.

In three of eight patients successfully treated by us, the stepwise increase in PaO_2 with increasing levels of PEEP was quite striking. In two of these patients (Cases 6 and 7), the PaO_2 rose from 79 and 160 mm Hg without PEEP to 418 and 481 mm Hg, respectively, with 15 cm H_2O PEEP. With 15 cm H_2O PEEP, it became possible to lower the FIO_2 from 0.96 to 0.38 and maintain PaO_2 greater than 60 mm Hg in both of these patients. Chest x-ray films in Case 7, before (Fig 7A) and after 12 hours of PEEP (Fig 7B) revealed a dramatic clearing of the interstitial infiltrate. A progressive improvement in PaO_2 occurred over this time while on FIO_2 of 0.38. Over the course of 48 hours, the PaO_2 steadily increased, permitting a progressive reduction in PEEP and eventual cessation of treatment. Each time the level of PEEP was reduced the PaO_2 fell, but this decline was less over the course of treatment (Fig 6). A third patient (case 8) was likewise successfully treated with prolonged 15 cm H_2O PEEP; in this patient, however, FIO_2 of 0.6 was required for 24 hours, at which time it became possible to lower the FIO_2 to 0.38 and then gradually reduce the level of PEEP.

Respiratory Distress Syndrome in Adults

Clinical Picture

The respiratory distress syndrome in adults is a term recently adopted to encompass a clinical
INDICATIONS AND PHYSIOLOGIC CONSIDERATIONS OF PEEP

Figure 6. Progressive improvement in PaO₂ in patients TM (Case 6) and WG (Case 7). The PaO₂ could only be initially maintained above 60 mm Hg (horizontal hash marks) with a fraction of inspired oxygen (FiO₂) of 0.38 when 15 cm H₂O PEEP was used. Over 48 hours, the steady increase in PaO₂ permitted a progressive reduction and eventual cessation of PEEP. Although the PaO₂ fell each time the level of PEEP was reduced, it was continuously maintained above 60 mm Hg. (Reprinted with permission of the Journal of Trauma.)

These pressures required to ventilate the lung are high (40-80 cm H₂O) for tidal volumes of 500 to 800 ml indicating a marked decrease in lung compliance. It is almost impossible to let the patient use the assist mode of ventilation since his respiratory rate exceeds the capability of most ventilators; hence, sedation and/or muscle relaxant drugs are used. Some patients show improvement in the PaO₂ following institution of mechanical ventilation, but most show little or no improvement and follow a relentless course of progressive hypoxemia, to death. Oxygen toxicity probably contributes to the progressive hypoxemia since high inspired oxygen concentrations are maintained for many days. It is now our practice to utilize PEEP if there is not an immediate and significant improvement within 12 hours of instituting IPPB continuous ventilatory support. There are many minor and major variations of the clinical picture outlined above, and these are beautifully presented in two monographs which are recommended to the reader.

 syndrome which had previously been labeled "post-traumatic pulmonary insufficiency," "DaNang lung," "shock lung" and "congestive atelectasis." The syndrome develops in a previously healthy patient who suffers pulmonary or nonpulmonary trauma, either accidental or surgical, and has an episode of shock (septic or hemorrhagic) which responds to blood and fluid replacement and/or pressor drugs. Some hours following recovery, when the patient appears to be stable, tachypnea develops and rales are noted throughout the lungs. Arterial PaO₂ on room air or supplemental oxygen is significantly reduced (40-60 mm Hg range) and the PaCO₂ is low. The hypoxia is uncorrected by administration of 100 percent oxygen, indicating intrapulmonary right-to-left shunting due to areas of the lung which are perfused but not ventilated. The patient is usually severely distressed because of marked dyspnea and tachypnea. Tracheal intubation is frequently performed at this time and mechanical ventilation instituted.

Figure 7A (left). Chest x-ray film of case 7 before applications of PEEP. (Reprinted with permission of the Journal of Trauma.) 7B (right). Chest x-ray film of case 7 following 12 hours PEEP. (Reprinted with permission of the Journal of Trauma.)
Pathophysiology of the Respiratory Distress Syndrome in Adults

The precise sequence of events which lead to the RDSA remains to be determined. Pathologic studies of the lungs of patients dying with RDSA are difficult to relate to the acute clinical picture since most patients survive long enough to develop other pathologic findings secondary to infection, oxygen toxicity, tracheal suctioning, etc. At the time of onset of respiratory distress, there is usually a diffuse interstitial and alveolar pattern on the chest roentgenogram without cardiomegaly or enlargement of the pulmonary vessels which has been called noncardiac pulmonary edema. These roentgenographic findings suggest an increased amount of fluid in the lung. If true, we must assume that the fluid leaks into the interstitium and alveoli due to loss of functional integrity of the alveolar capillary membrane and not due to left ventricular failure. This conclusion is based on the fact that pulmonary artery and wedge pressures have been normal in all our patients and that pulmonary edema secondary to transient left ventricular failure or pulmonary venous hypertension usually clears rapidly, and is accompanied by only mild hypoxia which is easily corrected by increasing the inspired oxygen concentration. Further, there is usually only a minimal decrease in lung compliance in patients with pulmonary edema secondary to left ventricular failure. How, then, can we tie together the observed physiologic aberrations in the RDSA viz 1) severe hypoxia uncorrected by 100 percent oxygen, indicating lung units that are perfused but not ventilated (right-to-left shunt); 2) decreased lung compliance which of necessity leads to a decreased functional residual capacity?

If fluid leaks into the alveolar space, it could exclude ventilation by its physical presence (Fig 10A); displace or inhibit surfactant which would decrease the stability of the alveoli and promote atelectasis; and/or decrease lung compliance and therefore functional residual capacity. Other primary or contributory factors might include collapse of the respiratory bronchiole due to inhibition or displacement of surfactant, or obstruction of the respiratory bronchiole by stable foam or bubbles. Small pulmonary emboli, ie fibrin clots, particulate material from intravenous fluids, etc have been suggested as possible primary or secondary etiologic factors. This suggestion is based on experimental work in animals wherein particulate emboli (barium sulfate) caused alveolar duct constriction resulting in a decreased compliance, re-

POSSIBLE MECHANISMS FOR HIGH R-L SHUNT IN RESPIRATORY DISTRESS SYNDROME

Figure 8. A schematic diagram of alveoli, alveolar duct and respiratory bronchiole to represent the theoretic pathophysiology in the acute respiratory distress syndrome. Fluid filling the alveoli excluding ventilation, interstitial and alveolar edema inhibiting surfactant leading to atelectasis, either directly or indirectly through collapse of the terminal or respiratory bronchiole.

Figure 9. Functional residual capacity (FRC) in liters before, after one hour of, and one hour after application of 5 cm Hg O PEEP. (Reprinted with permission of the Canadian Anaesthetists' Society Journal, 16:483, 1969.)
duced functional residual capacity and probably hypoxia although the authors did not measure arterial blood gases. This mechanism remains speculative since pulmonary emboli have not been demonstrated in the lungs of patients dying of the RDSA and no one has demonstrated that alveolar duct constriction occurs in man.

Possible Mechanisms for PEEP’s Effectiveness

Reversal of Hypoxemia

Since we are not certain of the pathophysiologic sequences in the RDSA, discussion of the manner in which PEEP affects these patients is speculative. We do know now that PEEP: 1) increases $PaO_2$; 2) increases functional residual capacity (Fig 9) proportional to the increase in PEEP; and 3) increases static lung compliance proportional to the level of PEEP.

If alveolar duct constriction plays a role it could explain the decreased compliance, decreased lung volume and probably the hypoxia; since in the animal studies these were all reversed by hyperinflation of the lung, one could assume that PEEP would do likewise. Unfortunately, blood gases were not measured in these animals, but the authors presumed that hypoxemia would result. Patients with RDSA have frequently received intravenous fluids or blood, and particulate or fibrin microemboli are possible. The pathologic changes in the lungs of the patients we have seen dying with RDSA are not characterized by microemboli, although disseminated intravascular coagulation was present in one case. It would seem that alveolar duct constriction may be a contributing factor, but probably is not responsible for the entire picture.

Fluid filling the alveolar spaces and hence excluding gas, atelectasis secondary to displacement or inhibition of surfactant, collapse or obstruction of the respiratory bronchiole could all result in hypoxemia if perfusion of these areas continues (right-to-left shunt). If fluid filling the alveoli is responsible for hypoxemia, PEEP might increase the volume of the alveoli so that the fluid no longer completely fills the alveoli and some gas exchange could occur (Fig 10). Collapse or obstruction of the respiratory bronchiole might be overcome by the increase in lung volume and increase in airway diameter allowing gas to enter the alveoli (Fig 10). If atelectasis secondary to loss or inhibition of surfactant is the mechanism for hypoxia, then PEEP might alone or with IPPB allow the critical opening pressure to be reached in the airway so that the atelectatic areas would be inflated. Further, with the maintenance of PEEP, the functional residual volume increases so that the IPPB would be inflating the lung at a different portion of the pressure-volume curve where airway pressure is always positive and collapse would be prevented. We are assuming that atelectasis of a portion of a lung acts in a manner similar to atelectasis of an entire lung wherein no volume change occurs until a critical opening pressure is reached, after which each increment of pressure change causes an increase in volume.

Effects on Cardiac Output

Although clinical improvement and elevation of the $PaO_2$ has been well documented by all who have studied PEEP, some investigators have reported a significant reduction in cardiac output with its use, whereas others have not seen this complication. Courmand demonstrated that in normal individuals, cardiac output would be decreased by IPPB if improper mask pressure configuration was employed. It has also been shown...
that hypovolemia and/or decreased vasomotor tone secondary to deep anesthesia causes a fall in blood pressure, even with low mask pressures (1-5 mm Hg) and proper pressure configurations. Since in adults, PEEP has only been used in conjunction with IPPB, the same precautions one uses with IPPB must be exercised.

Positive pressure ventilation decreases cardiac output by decreasing the inflow of blood into the right heart by increasing intrapleural pressure and compressing the major veins. It has been shown that the higher the mask mean pressure or airway pressure, the greater the decrement in cardiac output in normal individuals. In patients with high total pulmonary resistance or airway resistance one would assume that more of the peak pressure is dissipated in overcoming the resistance and very little will be transmitted to the intrapleural space. Hence, the same peak pressure that would cause a marked decrease in cardiac output in a normal person might have little effect in the patient with high total pulmonary resistance. PEEP, on the other hand, is a steady state pressure and hence, its transmission to the intrapleural space would be unaffected by airway resistance and only modified by the compliance (elastic forces) of the lung. As Fenn pointed out many years ago, as the lung expands, the intrapleural pressure becomes more negative for each increment in volume so that less positive pressure would be sensed in the intrapleural space.

In our study, no patient had a significant change in cardiac output with PEEP (Fig 11). As predicted, only a small fraction of the positive end-expiratory pressure was transmitted to the venous system. For example, in case 6, the wedge and central venous pressures rose only 2 cm H$_2$O with 5 cm H$_2$O PEEP, 3.5 cm H$_2$O for 10 cm H$_2$O PEEP, and 5 cm H$_2$O for 15 cm H$_2$O PEEP (Fig 12). The rise in wedge pressure was matched by an equivalent rise in pulmonary artery pressure; thus, since no significant change in cardiac output occurred with PEEP, there was no significant change in pulmonary resistance. Hence, if the patient needs PEEP and has evidence of a decreased pulmonary compliance and FRC, there will be minimal changes in systemic or pulmonary artery blood pressure or cardiac output providing the patient is not hypovolemic and that extremely high levels of PEEP (such as 20 and 24 cm H$_2$O) are not used.

Serial measurements of mixed venous oxygen tension (PvO$_2$) or oxygen content (CvO$_2$), in addition to frequent arterial blood pressure deter-
minations and hourly urine volumes, would serve a useful purpose for those using PEEP without the facilities for cardiac output measurements. Should the $P_{\text{VO}_2}$ or $C_{\text{VO}_2}$ suddenly fall with PEEP on and rise with PEEP off, then, assuming little change in oxygen consumption or arterial pH, there would probably have been a significant fall in cardiac output with PEEP (see article by Keighley, this issue). We believe that this phenomenon is relatively uncommon if the patient is not hypovolemic and has the type of pulmonary injury that requires PEEP.

Systemic Oxygen Transport and Tissue Oxygenation

Improvement of systemic oxygen transport, the product of cardiac output and arterial oxygen content, is the truly important goal of PEEP since it reflects the state of tissue oxygenation better than arterial oxygen content alone. Particularly, it is important to maintain adequate oxygen delivery with lower inspired oxygen concentrations to avoid oxygen toxicity.

Lutch,24 studying a group of patients he diagnosed as having "the stiff thorax syndrome" (it was not clear from his description that they had RSDA) demonstrated a mean fall in cardiac index for the group. However, some of the patients actually had an increase in cardiac index. Although oxygen transport decreased in their patients, it was adequate for the measured oxygen consumption, and therefore they concluded that "total body tissue oxygenation was probably not impaired."

PEEP Versus Retard

On some ventilators, it is possible to retard expiratory flow, raising the mean airway pressure, yet permit the end-expiratory pressure to return to zero cm H$_2$O for a short moment. Cheney and Burnham25 have shown in dogs with experimental interstitial pulmonary edema from oleic acid that the pulmonary "retard" is no more effective than IPPB and not as valuable as PEEP in reducing pulmonary shunt or increasing PaO$_2$. Furthermore, use of high tidal volumes and a large minute ventilation were also not as effective as PEEP.

Complications

Kumar et al7 reported three cases of mediastinal emphysema and one case of tension pneumothorax while PEEP was being used. In our original study, no complications developed while PEEP was being used; however, pneumothorax did occur in one patient (case 8) two days after treatment had been discontinued. Since the study, we have treated several dozen patients; several patients developed a pneumothorax and one a pneumomediastinum. It is not clear whether pneumothorax occurs more frequently with PEEP than IPPB; however, in both instances, it represents a major crisis since it is quickly converted from a simple to a tension pneumothorax. It is therefore necessary to immediately insert a large lumen tube into the pleural space and attach it to suction so that a tension pneumothorax can be prevented. A pneumothorax which is properly drained is not an absolute contraindication to the use of PEEP especially if removal of PEEP causes severe hypoxia or requires dangerously high inspired oxygen concentrations to maintain adequate arterial partial pressure of oxygen (>60 mm Hg). We have successfully maintained one patient on PEEP for 14 days after development of a bilateral pneumothorax. If one, however, can reduce or discontinue PEEP without the patient developing hypoxia, it should decrease the duration of the pneumothorax.

Other Therapeutic Measures

Additional therapeutic maneuvers considered beneficial by others are: 1) reduction of the increased extravascular lung water by administering potent diuretics and albumin to raise the plasma colloid osmotic pressure,26 2) the use of high dosage corticosteroids,3 3) appropriate antibiotics for systemic and pulmonary infections. It seems likely that a reasonable therapeutic program, including the judicious use of PEEP, will significantly reduce the unacceptably high mortality from this major pulmonary complication of injury and shock.

Summary

PEEP is an important therapeutic tool for treating patients with the respiratory distress syndrome of adults. It reverses the severe hypoxemia, large (A-a) $O_2$ gradient, decreased functional residual capacity and compliance immediately. It also seems to produce a more gradual improvement in oxygenation over 12-48 hours. Currently, it has been used only for patients with RSDA and does not appear to be indicated for other lung diseases.

References

24 Lutch JS, Murray JF: Continuous positive pressure ventilation: effects on systemic oxygen transport and tissue oxygenation. Ann Int Med 76:193, 1972