saturated binding capacity in the present report has been matched only in some Scandinavian subjects in whom an antibody to transcobalamin II developed after injections of depot preparations of vitamin B_{12}[26] and in a patient with the unexplained presence of an unusual transcobalamin[27] that appears to be a complex of transcobalamin II. In neither case was the type of binder abnormality similar to the present one.

I am indebted to Ms. Lynn Baril for technical assistance.

References

1. Hall CA: Transport of vitamin B_{12} in man. Br J Haematol 16:429-433, 1969
2. Carmel R: Vitamin B_{12}-binding protein abnormality in subjects without myeloproliferative disease. II. The presence of a third vitamin B_{12}-binding protein in serum. Br J Haematol 22:53-62, 1972
3. Simons K: Gastric intrinsic factor and other vitamin B_{12} transport proteins: chemical and physiologic properties, Progress in Gastroenterology. Vol I. Edited by GB Jerzy Glass. New York, Grune and Stratton, 1968, pp 195-220
4. Meyer LM, Bertcher RW, Cronkite EP, et al: Co^{60} vitamin B_{12} binding capacity of serum in persons with hematologic disorders, various medical diseases and neoplasms. Acta Med Scand 169:557-575, 1961
5. Herbert V: Diagnostic and prognostic values of measurement of serum vitamin B_{12}-binding proteins. Blood 32:305-312, 1968
6. Chikkappa G, Corcino J, Greenberg ML, et al: Correlation between various blood white cell pools and the serum B_{12}-binding capacities. Blood 37:142-151, 1971
7. Carmel R: Vitamin B_{12}-binding protein abnormality in subjects without myeloproliferative disease. I. Elevated serum vitamin B_{12}-binding capacity levels in patients without leucocytosis. Br J Haematol 22:43-51, 1972
8. Carmel R, Coltman CA Jr: Radioassay for serum vitamin B_{12} with the use of saliva as the vitamin B_{12} binder. J Lab Clin Med 74:967-975, 1969
9. Carmel R: The vitamin B_{12}-binding proteins of saliva and tears and their relationship to other vitamin B_{12} binders. Biochim Biophys Acta 263:747-752, 1972
10. Carmel R, Coltman CA Jr: Monocytic vitamin B_{12}-binding protein. Blood 37:360-366, 1971
11. Silverstein E, Herbert V: Rapid determination of vitamin B_{12}-binding α and β globulin in serum. Blood 31:518-521, 1968
12. Carmel R: A rapid ammonium sulfate precipitation technic for separating serum vitamin B_{12}-binding proteins: method and applications. Am J Clin Pathol 62:367-372, 1974
13. Carmel R, Coltman CA Jr: Nonleukemic elevation of serum vitamin B_{12} and B_{12}-binding capacity levels resembling that in chronic myelogenous leukemia. J Lab Clin Med 78:289-297, 1971
14. Hall CA, Wanko M: Increased transcobalamin I in a leukemoid reaction. J Lab Clin Med 78:298-301, 1971
15. Beard MF, Pitney WR, Sanneman EH: Serum concentrations of vitamin B_{12} in patients suffering from leukemia. Blood 9:789-794, 1954
16. Miller A: The *in vitro* binding of $cobalt^{60}$ labeled vitamin B_{12} by normal and leukemic sera. J Clin Invest 37:556-566, 1958
17. Hall CA, Finkler AE: Vitamin B_{12}-binding protein in polycythemia vera plasma. J Lab Clin Med 73:60-69, 1969
18. Simons K, Weber T: The vitamin B_{12}-binding protein in human leukocytes. Biochim Biophys Acta 117:201-208, 1966
19. Carmel R, Herbert V: Vitamin B_{12}-binding protein of leukocytes as a possible major source of the third vitamin B_{12}-binding protein of serum. Blood 40:542-549, 1972
20. Corcino J, Krauss S, Waxman S, et al: Release of vitamin B_{12}-binding protein by human leukocytes in vitro. J Clin Invest 49:2250-2255, 1970
21. Waxman S, Gilbert HS: A tumor-related vitamin B_{12}-binding protein in adolescent hepatoma. N Engl J Med 289:1053-1056, 1973
22. Burger RL, Waxman S, Gilbert HS, et al: Isolation of a novel B_{12}-binding protein associated with adolescent hepatomas. J Clin Invest 53:13a, 1974
23. Grossowicz N, Hochman A, Aronovitch J, et al: Malignant growth in the liver and serum-vitamin-B_{12} levels. Lancet 1:1116-1117, 1957
24. Retief FP, Vandenplas L, Visser H: Vitamin B_{12} binding proteins in liver disease. Br J Haematol 16:231-240, 1969
25. Schønau Jørgensen F: Vitamin B_{12} and its binding proteins in cirrhosis and infectious hepatitis. Scand J Haematol 7:322-324, 1970
26. Schwartz M, Bastrup-Madsen P: A new vitamin B_{12} binding protein in serum causing excessively high serum vitamin B_{12} values. Scand J Haematol 5:35-40, 1968
27. Carmel R, Tatsis B: An abnormal serum transcobalamin with fast γ-globulin electrophoretic mobility associated with very high serum B_{12} levels. Clin Res 21:831, 1973

OPTIMUM END-EXPIRATORY AIRWAY PRESSURE IN PATIENTS WITH ACUTE PULMONARY FAILURE

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Abstract To determine whether in the management of pulmonary failure, the maximum compliance produced by positive end-expiratory pressure coincides with optimum lung function, 15 normovolemic patients requiring mechanical ventilation for acute pulmonary failure were studied. The end-expiratory pressure resulting in maximum oxygen transport (cardiac output times arterial oxygen content) and the lowest dead-space fraction both resulted in the greatest total static compliance. This end-expiratory pressure varied between 0 and 15 cm of water and correlated inversely with functional residual capacity at zero end-expiratory pressure ($r = -0.72$, $p < 0.005$). Mixed venous oxygen tension increased between zero end-expiratory pressure and the end-expiratory pressure resulting in maximum oxygen transport, but then decreased at higher end-expiratory pressures.

When measurements of cardiac output or of true mixed venous blood are not available, compliance may be used to indicate the end-expiratory pressure likely to result in optimum cardiopulmonary function. (N Engl J Med 292:284-289, 1975)

ACUTE pulmonary parenchymal failure is characterized by a decreased functional residual capacity (FRC),[1-3] a decrease in lung compliance,[1,4] and increased venous admixture that is mainly due to direct right-to-left shunting through nonventilated lung segments.[4] These changes are caused by consolidation of lung tissue (secondary to pneumonia, congestion, or atelectasis) or by interstitial changes (i.e., edema, infiltrates, or fibrosis).

Previous investigators[2,3,5-8] have advocated the use of large tidal ventilation or application of a positive end-expiratory pressure (PEEP), or both, for the treatment of acute pulmonary failure. PEEP may act to produce both beneficial and detrimental effects: first of all, PEEP recruits atelectatic areas for gas exchange, thereby increasing the FRC, compliance and arterial oxygen

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Abbreviations Used

$AaDO_2$:	alveolar to arterial oxygen tension difference
$avDO_2$:	arteriovenous oxygen content difference
C_aO_2:	arterial oxygen content
CT:	lung and chest-wall (static) compliance
C_vO_2:	mixed venous oxygen content
FI_{O_2}:	inspired oxygen concentration
FRC:	functional residual capacity
$PaCO_2$:	arterial carbon dioxide tension
PaO_2:	arterial oxygen tension
PE_{CO_2}:	mixed expired carbon dioxide
PEEP:	positive end-expiratory pressure
pHa:	arterial pH
pHv:	mixed venous pH
$PvCO_2$:	mixed venous carbon dioxide tension
PvO_2:	mixed venous oxygen tension
$\dot{Q}_S/\dot{Q}_T$:	intrapulmonary shunt fraction
$\dot{Q}_T$:	cardiac output
$V_{D\,alv}$:	alveolar dead space
$V_{D\,anat}$:	anatomic dead space
$V_{D\,phys}$:	physiologic dead space
$V_{D\,shunt}$:	dead-space effect of $\dot{Q}_S/\dot{Q}_T$
V_T:	tidal volume
ZEEP:	zero end-expiratory pressure

tension[2,3,7]; secondly, it may overdistend alveoli, thereby decreasing compliance and eventually cause disruption and pneumothorax[2]; thirdly, it may obstruct venous return and so decrease cardiac output.[2,7,9-11]

Whether PEEP increases or decreases compliance depends on the relative contributions of recruitment of atelectatic areas and of overdistention of alveoli. Sufficiently high PEEP must preferentially overdistend all alveoli, with a consequent decrease in compliance, increase in physiologic dead space, and decrease in cardiac output. In contrast, lower levels of PEEP might produce more recruitment than overdistention. This reasoning suggests that the maximum compliance produced by PEEP should coincide with optimum lung function. If so, compliance could be used as a simple indicator of the level of PEEP that would produce optimum pulmonary gas exchange.

Methods

We studied 15 patients requiring continuous mechanical ventilation for acute respiratory failure. This group consisted of 13 men and two women ranging in age from 24 to 74 years (mean, 49 years). Respiratory failure followed massive trauma in five patients, a major surgical procedure in three, and either metabolic or infective processes in the remainder. An inspired oxygen concentration (FI_{O_2}) of 21 to 75 per cent was used to maintain the arterial oxygen tension (PaO_2) at zero end-expiratory pressure (ZEEP) between 55 and 92 torr. For a given patient, this FI_{O_2} was maintained throughout the study. A volume-controlled ventilator (Ohio 560), on assisted mode, was used to deliver a constant tidal volume of 13 to 15 ml per kilogram at a constant inspiratory flow rate throughout the study. PEEP was applied with an Emerson PEEP Assembly.

Arterial catheter and Swan—Ganz pulmonary-artery line were inserted for diagnostic and therapeutic purposes. Intravascular-fluid volume was adequate, as judged by normal central venous and pulmonary capillary "wedge" pressures. No study was conducted before the second day of ventilator treatment. The patients were supine with the head slightly elevated.

Base-line measurements were obtained at ZEEP. PEEP was then applied in increments of 3 cm of water and the measurements repeated after 15 to 20 minutes' stabilization at each level of PEEP. The study continued to a level of PEEP that markedly decreased cardiac output. This end point ranged between 6 and 18 cm of water. Control measurements were then repeated at ZEEP.

Measurements

Total *lung and chest wall (static) compliance* (CT) was assessed from simultaneous recordings of expired tidal volume and airway pressure. We calculated CT by dividing the tidal volume by the difference between a "plateau" pressure at end inspiration (resulting from a period of no-flow of 1 to 1.5 seconds) and end-expiratory pressure. Tidal volume was not permitted to vary more than ± 20 ml to eliminate changes in CT due to changes in tidal volume.[12]

FRC was determined by helium dilution.[13] A series of one-way valves and a bag-in-the-box device were included in the closed circuit. This procedure permitted the patient's own ventilator to compress the bag-in-the-box, thus assuring ventilatory patterns (frequency, tidal volume) nearly identical to those normally used in the absence of a closed circuit. The results were compared to the predicted normal values in the supine position.[14,15]

Cardiac output ($\dot{Q}_T$) was measured in duplicate at each level of PEEP by dye dilution, with use of indocyanine green and a Waters densitometer.

pH and blood gas tensions from arterial (PaO_2, $PaCO_2$, pHa) and mixed venous blood (PvO_2, $PvCO_2$, pHv), and mixed expired carbon dioxide (PE_{CO_2}) were determined by standard electrode technics and corrected for the patient's temperature.[16] Hemoglobin and hemoglobin oxygen saturation were measured by a CO-Oximeter (Instrumentation Laboratories). From these measurements we calculated arterial and mixed venous oxygen content (C_aO_2, C_vO_2), arteriovenous oxygen content difference ($avDO_2$), alveolar to arterial oxygen tension difference ($AaDO_2$), and intrapulmonary shunt fraction ($\dot{Q}_S/\dot{Q}_T$).[17,18]

Systemic oxygen transport (in milliliters per minute) was obtained from $\dot{Q}_T$ and C_aO_2: $\dot{Q}_T$ (liters per min) × C_aO_2 (ml per liter).

Total or physiologic dead space/tidal volume ratio ($V_{D\,phys}/V_T$) was determined by the Enghoff modification of the Bohr equation.[19] Anatomic dead space ($V_{D\,anat}$) was measured by the single-breath nitrogen-washout technic.[20] The dead-space effect of $\dot{Q}_S/\dot{Q}_T$ ($V_{D\,shunt}$) was determined by the approach proposed by Kuwabara.[21] Alveolar dead space ($V_{D\,alv}$) was calculated with the formula: $V_{D\,phys} - V_{D\,shunt} - V_{D\,anat}$

Airway resistance was estimated by the Rattenborg method[22]: the difference between peak airway pressure and "plateau" pressure at end-inspiration was divided by the flow provided by the ventilator at the moment of peak pressure. Flow was calculated from volume and inspiratory time. The end-inspiratory flow is lower than this average for the whole of inspiration, owing to the response of the ventilator to peak pressure. A correction factor was obtained by mechanical analogue studies and was applied to all calculated flows. The magnitude of the correction varied with peak pressure but approximated −10 per cent. The directional effect of this correction was to decrease flow and therefore to increase the value for resistance as PEEP increased.

Uneven distribution of ventilation was assessed by the single-breath nitrogen-washout test.[23] The per cent change in nitrogen concentration on the "nitrogen plateau" (phase III) over an exhaled volume of 500 ml gives an estimate of the evenness of ventilation and, in normal spontaneously breathing subjects, is less than 2 per cent. The results are independent of functional residual capacity (FRC) and tidal volume.[24]

Statistical analysis was performed with Student's t-test and the method of least squares for regression.[25]

Results

Systemic oxygen transport and FRC. Application of PEEP increased oxygen transport in 13 of the 15 patients studied. Oxygen transport increased progressively up to a lev-

el of PEEP that varied from patient to patient, and then decreased at higher levels. For the purposes of this study, the level of PEEP coinciding with the maximum oxygen transport was taken as a reference point for all other PEEP levels, and was termed "best PEEP." "Best PEEP" varied widely among patients, ranging between 0 and 15 cm of water (Fig. 1). In patients with abnormally low FRC values at ZEEP, maximum oxygen transport was achieved at higher levels of PEEP than in patients with normal or high FRC values (Fig. 2), resulting in a loose negative correlation between "best PEEP" and initial FRC ($r = -0.72$, $p < 0.005$).

The increase in oxygen transport was mainly due to an increase in C_aO_2 (Fig. 3). Conversely, the decrease at higher levels of PEEP was due to a decrease in cardiac output.

Blood gas tensions and derived measurements. PaO_2 increased, and $\dot{Q}_S/\dot{Q}_T$ decreased with rising PEEP at all levels, but did not correlate with oxygen transport or the decrease in cardiac output at higher PEEP (Fig. 4 and 5). PvO_2 increased significantly between 6 cm of water below

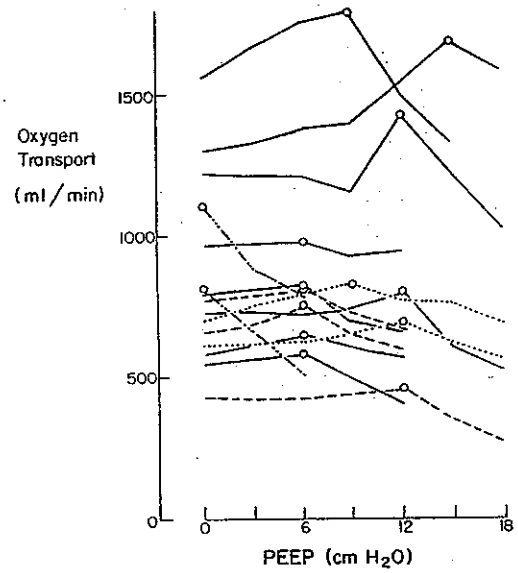

Figure 1. Effect of Varying Levels of PEEP on Oxygen Transport in All Patients Studied.

The point of maximum oxygen transport is indicated (o). Differing lines are used merely to distinguish individual patients.

"best PEEP" and "best PEEP," where it reached its highest value (Fig. 4). Higher levels of PEEP decreased PvO_2.

Total compliance. CT changes paralleled the changes in systemic oxygen transport (Fig. 3). CT increased significantly with each 3-cm-of-water increment of PEEP up to the level of maximum oxygen transport (from 41 ±4 ml per centimeter of water at zero end-expiratory pressure to 51 ± 4 ml), did not change significantly between "best PEEP" and 3 cm of water above, and decreased at 6 cm of water above "best PEEP."

Dead space. $V_{D phys}/V_T$ decreased with the application of PEEP in 13 of the 15 patients. The mean value fell from 0.42 ± 0.02 at ZEEP to 0.36 ± 0.02 at "best PEEP" and

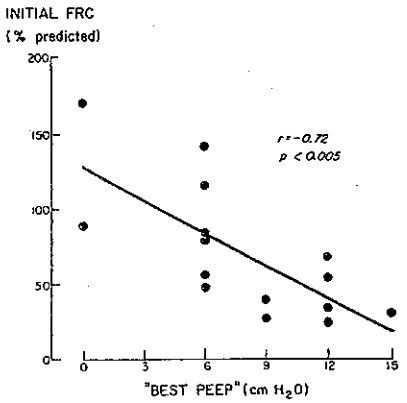

Figure 2. Relation between Functional Residual Capacity (FRC) Measured at Zero End-expiratory Pressure, and the Amount of PEEP Resulting in Optimum Oxygen Transport ("Best PEEP").

Each point represents the data of one patient.

increased to 0.40 ± 0.03 at 6 cm of water above this level (Fig. 5). $V_{D alv}/V_T$ showed the same directional changes as $V_{D phys}/V_T$ reaching the lowest value at "best PEEP" and increasing at still higher levels. The changes in $V_{D alv}$ with increments of PEEP correlated with two variables: increases in compliance were associated with decreases in $V_{D alv}/V_T$ and vice versa ($r = -0.87$; $p < 0.001$); and there was also an inverse relation between changes in car-

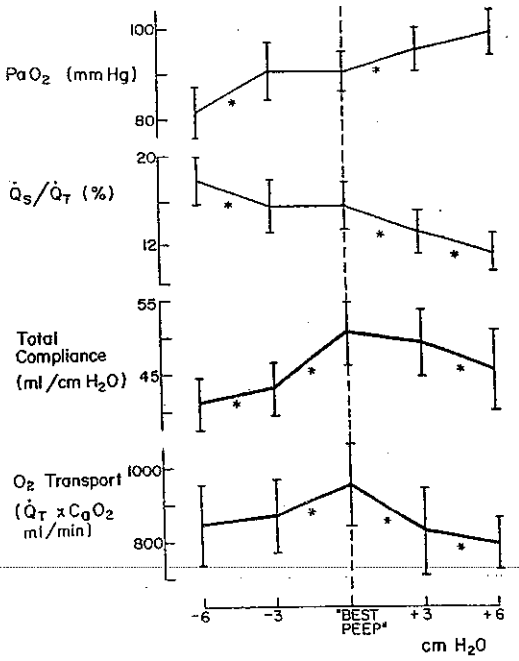

Figure 3. Mean Values ± S.E. of Arterial Oxygen Tension (PaO_2), Intrapulmonary Shunt ($\dot{Q}_S/\dot{Q}_T$), Total Static Compliance, and Oxygen Transport, Measured at the Level of PEEP Resulting in Maximum Oxygen Transport ("Best PEEP"), Compared to Values Obtained at 3 and 6 Cm of Water of PEEP below (−3, −6) and above (+3, +6) That Level.

*Significant changes ($p < 0.05$) at each 3-cm-of-water increment of PEEP.

output with PEEP and the changes in $V_{D alv}/V_T$ ($r = -0.82$; $p < 0.001$). $V_{D anat}$ increased progressively with PEEP, the mean change being 3 ± 0.4 ml per cm of water of PEEP. $V_{D shunt}/V_T$ decreased with PEEP. However, this value was small (Table 1).

Airway resistance. Flow resistance at end-inspiration decreased progressively with PEEP. The mean decrease was 0.3 ± 0.1 cm of water per liter per second per centimeter of water of PEEP.

Uneven distribution of ventilation. Distribution of the inspired gas was more even with PEEP. The mean increase in nitrogen concentration during phase III of a single-breath washout decreased from 7.5 ± 1.0 per cent per 500 ml at ZEEP to 6.5 ± 1.5 per cent at 6 cm of water of PEEP, and to 5.2 ± 1.2 per cent at 12 cm of water.

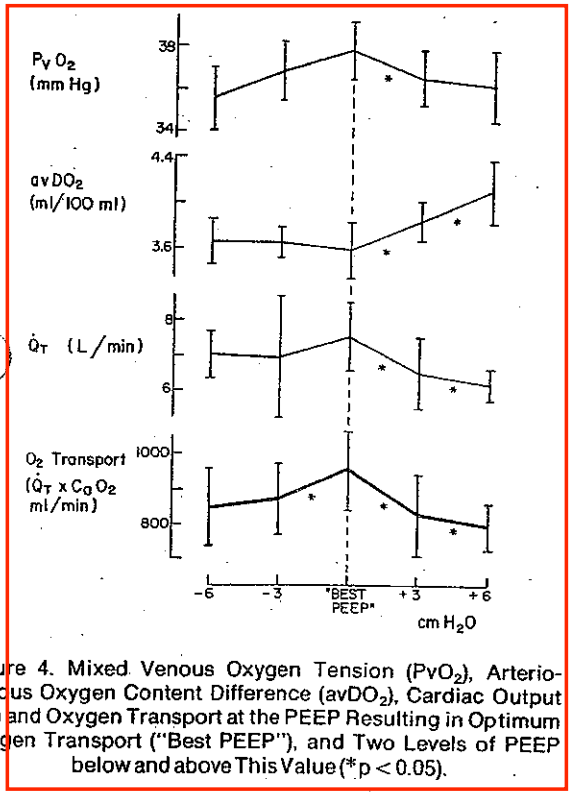

Figure 4. Mixed Venous Oxygen Tension (PvO_2), Arteriovenous Oxygen Content Difference ($avDO_2$), Cardiac Output ($\dot{Q}_T$) and Oxygen Transport at the PEEP Resulting in Optimum Oxygen Transport ("Best PEEP"), and Two Levels of PEEP below and above This Value (*$p < 0.05$).

We calculated means and standard errors of the results obtained at "best PEEP," at a level below and above this level and ZEEP (Table 1). These findings suggest that at "best PEEP," optimum values were reached for oxygen transport, CT, PvO_2, $V_{D phys}/V_T$ and $V_{D alv}/V_T$.

Discussion

Previous authors have assessed the efficiency of oxygen delivery, in response to the application of PEEP, by using the arterial oxygen tension, $AaDO_2$ or $\dot{Q}_s/\dot{Q}_T$ as index.[2,6] This approach has been questioned,[26] since these values do not necessarily reflect situations in which oxygenation is inadequate owing to hypoperfusion, a possible complication of this form of treatment. Two recent studies[10,11] assessed the beneficial effect of PEEP by determining the volume of oxygen transported to the tissue per unit time.

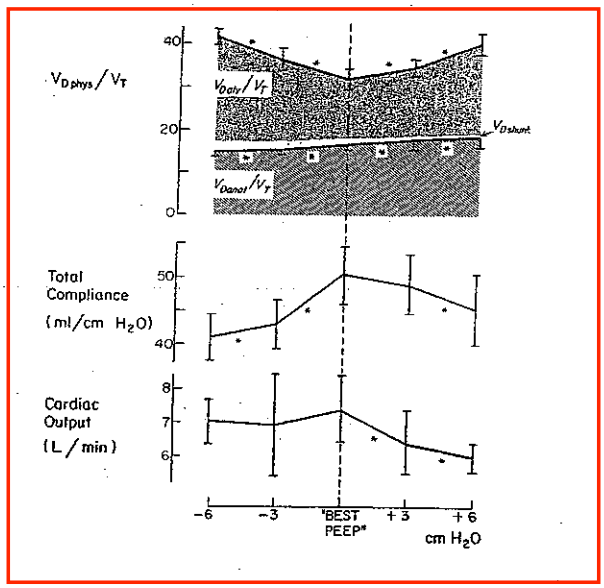

Figure 5. Changes in Physiologic Dead Space ($V_{D phys}$) and Its Components, Cardiac Output and Compliance with Increments of PEEP (*$p < 0.05$).

This approach, in turn, reflects the amount of oxygen available to the consuming cell, and takes into account the combined effect of PEEP on arterial oxygen content and cardiac output but does not account for any increase in oxygen consumption that might be induced by PEEP, or for any inappropriate regional redistribution of blood flow. We have no data at present to indicate whether clinically important changes in regional blood flow occur with PEEP. However, we have not observed any clinical indication that this would be an over-riding consideration. Increases in oxygen consumption with PEEP appear to be minimal if present at all. Lutch and Murray[10] observed an unchanged oxygen consumption between zero and 15 cm of water end-expiratory pressure. In our series of clinically normovolemic patients, mixed venous oxygen tension reached a maximum value at the level of PEEP that resulted in the highest systemic oxygen transport, and $avDO_2$ remained unchanged up to this level of PEEP. This observation suggests that the increased oxygen transport associated with PEEP was not matched by an increase in oxygen consumption and thus implies an increase in oxygen availability with "best PEEP."

The above reasoning suggests that, for our patients, there indeed was a "best PEEP" — one that produced the greatest cardiopulmonary benefit as indicated by greatest oxygen transport. It should not be inferred from this hypothesis that all patients with pulmonary failure will be well served by PEEP. Patients with emphysema and an initially high FRC do not benefit from PEEP during acute respiratory failure.[27] Cardiac output and oxygen delivery decreased with PEEP in these patients. On the other hand, a patient with a markedly decreased FRC requires high levels of PEEP to achieve maximum oxygen transport (Fig. 2). The beneficial effect and optimum level of PEEP depend on the underlying pulmonary condition. A patient with a low FRC, with a consequent potential for recruitment of collapsed alveoli, may benefit from PEEP

Table 1. Summary of Results (Means ± S.E.).*

Measurement	ZEEP	6 cmH$_2$O <"Best PEEP"	"Best PEEP"	6 cmH$_2$O >"Best PEEP"
Oxygen transport (ml/min)	841±108†	858±90†	950±110	794±68‡
Static compliance (ml/cmH$_2$O)	41±4‡	41±4‡	51±4	45±5‡
PaO_2 (torr)	78±3‡	82±6‡	90±4	99±5†
PvO_2	35±1†	35±2†	38±1	36±1†
$AaDO_2$ (torr)	136±24†	140±32	125±23	108±19†
$\dot{Q}_s/\dot{Q}_T$	0.18±0.03‡	0.18±0.03‡	0.15±0.02	0.11±0.02†
$AvDO_2$ (ml/100 ml)	3.7±0.2	3.7±0.2	3.6±0.3	4.1±0.3†
$V_{D\,phys}/V_T$	0.42±0.02‡	0.42±0.02‡	0.36±0.02	0.40±0.03‡
$V_{D\,anat}/V_T$	0.14±0.01†	0.14±0.01†	0.17±0.01	0.19±0.01†
$V_{D\,alv}/V_T$	0.27±0.02‡	0.27±0.02‡	0.18±0.01	0.22±0.02†
$V_{D\,shunt}/V_T$	0.02±0.01†	0.02±0.01†	0.01	0.01
Airway resistance (cmH$_2$O/l/min)	8±2†	7±2†	5±2	4±2†
Rise in nitrogen plateau (%/500 ml)	7.5±1.0†	7.1±1.2†	6.4±1.5	5.0±1.4†

*Since "best PEEP" varied from 0 to 15 cmH$_2$O, the value for n available for paired t-testing differed at each level. However, all available pairs were used in each test.

†Significant difference from value at "best PEEP" ($p < 0.05$).

‡Significant difference from value at "best PEEP" ($p < 0.005$).

whereas a patient whose alveoli are near maximum expansion may be harmed by PEEP. Failure to discriminate between these possibilities may produce inconsistent results.[2,10,11] For instance, King[11] reported that mean oxygen delivery progressively decreased with increments of PEEP in a group of patients in acute respiratory failure. However, in fact, oxygen transport at 5 cm of water of PEEP improved in six of the 11 patients studied — at 10 cm in three, at 15 cm in two and at 20 cm in one.

One purpose of this study was to find a simple bedside measurement that would indicate the optimum level of PEEP for oxygen delivery in an individual patient. Our data suggest that arterial-blood gas measurements and derived calculations do not identify the level of PEEP resulting in maximum oxygen transport. Q_T and PvO_2 are useful measurements for this purpose, but accurate measurement of cardiac output or access to pulmonary arterial blood is not always readily obtained. The present data suggest that an optimal situation is achieved in acute pulmonary failure when tidal ventilation takes place on the steepest part of the patient's pressure-volume curve — that is, when the highest compliance is achieved. A stylized version of such pressure-volume curves is shown in Figure 6.

The observed changes in total compliance are probably due to alterations in lung compliance, because chest-wall compliance is constant in this range of intrathoracic volume.[28] A likely explanation of the changes in compliance is the increase in resting lung volume produced by the increase in airway pressure and the re-expansion of atelectatic areas by PEEP. This possibility is supported by the decreases in $V_{D\,alv}$ observed in the present study. A reduction in alveolar surface forces also could increase compliance in patients when their resting lung volume is increased toward a more "physiologic" level by PEEP.[29]

The changes in $V_{D\,alv}$ can be explained by the re-expansion of atelectatic areas at low levels of PEEP, with (at constant tidal volume) some of the inspired air being shifted from overdistended and unperfused low compliance alveoli toward these newly expanded perfused lung segments. At higher levels of PEEP, more and more alveoli will be overdistended and underperfused as a consequence both of the high intra-alveolar pressure and of the fall in cardiac output. This effect increases $V_{D\,alv}$.[30] The above hypothesis is supported by the following findings: $V_{D\,alv}$ changes in inverse proportion to changes in cardiac output, suggesting that a reduced perfusion increases $V_{D\,alv}$; and changes in compliance with increments of PEEP also are negatively correlated with $V_{D\,alv}$. This observation supports the concept of the recruitment of previously atelectatic areas leading to an increase in compliance and a decrease in $V_{D\,alv}$, whereas overdistention of alveoli decreases compliance and increases $V_{D\,alv}$.

Our finding that $V_{D\,anat}$ increases with a higher transpulmonary pressure has been described earlier.[31] This observation, together with our measured decrease in airway resistance, suggests distention of conducting airways. The increase in airway diameter may also have contributed to the improvement in distribution of ventilation suggested by the progressively smaller increase of nitrogen concentration during phase III observed in our patients.

The contribution of a right-to-left shunt to the alveolar-arterial carbon dioxide tension difference, and hence to $V_{D\,phys}$ calculations, is only important in patients with diseases causing unusually large shunts. In this group of patients with mean values of $\dot{Q}_s/\dot{Q}_T$ ranging between 0.11 and 0.18, the calculated contribution of this component was clinically unimportant.

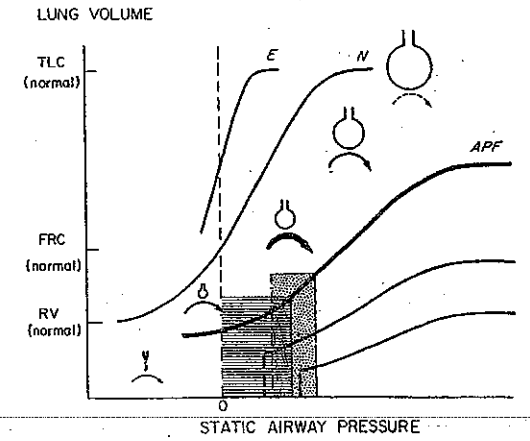

Figure 6. Family of Regional Pressure-Volume Curves of the Respiratory System, in Normal (N) Lungs and Those of Patients with Emphysema (E) and Acute Pulmonary Failure (APF).

The whole lung APF curve results from the sum of multiple regional compliance curves, some resembling normal and others from very low compliance regions, two of which are shown in the diagram. Shaded areas show pressure-volume relation during the same tidal ventilation, with and without PEEP. Broken vertical line denotes regional volume (RV) at which alveoli are unstable and readily "open" or "close." TLC represents total lung capacity.

This study suggests that, in normovolemic patients, total static compliance is a useful and simple means of finding the degree of lung distention that provides the best gas exchange with the least risk of alveolar overdistention and lung rupture. Although we have used the term "best PEEP," it should not be taken too literally. In this acute study, arterial oxygen transport and whole-body $avDO_2$ were optimum at this level, but it has been shown that a decrease in Q_T at a given level of PEEP may be offset by increasing intravascular volume (Pontoppidan H: Personal communication). We cannot extrapolate from these data to the assumption that the same changes necessarily occur in each vital organ, nor do we have information showing that these indexes are important variables indicating the optimum pattern for long-term ventilator management. However, the concept of not distending a lung beyond the point of maximum compliance, regardless of gas exchange, is probably reasonable from the standpoint of minimizing pulmonary damage, and, although such distention may be necessary transiently as an acute physical-therapy maneuver, we do not recommend its sustained use.

In the patients whom we studied, tidal volume was kept constant at all levels of PEEP; however, other variations are possible — e.g., a constant end-inspiratory pressure with variable PEEP and tidal volumes. We have not studied these possibilities, but the concepts outlined probably also apply under these circumstances.

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References

1. Ramachandran PR, Fairley HB: Changes in functional residual capacity during respiratory failure. Can Anaesth Soc J 17:359-369, 1970
2. Kumar A, Falke KJ, Geffin B, et al: Continuous positive-pressure ventilation in acute respiratory failure: effects on hemodynamics and lung function. N Engl J Med 283:1430-1436, 1970
3. Falke KJ, Pontoppidan H, Kumar A, et al: Ventilation with end-expiratory pressure in acute lung disease. J Clin Invest 51:2315-2323, 1972
4. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure in the adult. N Engl J Med 287:690-698, 743-752, 799-806, 1972
5. Hedley-Whyte J, Pontoppidan H, Morris MJ: The response of patients with respiratory failure and cardiopulmonary disease to different levels of constant volume ventilation. J Clin Invest 45:1543-1554, 1966
6. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. Lancet 2:319-323, 1967
7. McIntyre RW, Laws AK, Ramachandran PR: Positive expiratory pressure plateau; improved gas exchange during mechanical ventilation. Can Anaesth Soc J 16:477-486, 1969
8. Levine M, Gilbert R, Auchincloss JH Jr: A comparison of the effects of sighs, large tidal volumes, and positive end expiratory pressure in assisted ventilation. Scand J Respir Dis 53:101-108, 1972
9. Uzawa T, Asbaugh DG: Continuous positive-pressure breathing in acute hemorrhagic pulmonary edema. J Appl Physiol 26:427-432, 1969
10. Lutch JS, Murray JF: Continuous positive-pressure ventilation: effects on systemic oxygen transport and tissue oxygenation. Ann Intern Med 76:193-202, 1972
11. King EG, Jones RL, Patakas DA: Evaluation of positive end-expiratory pressure therapy in the adult respiratory distress syndrome. Can Anaesth Soc J 20:546-558, 1973
12. Visick WD, Fairley HB, Hickey RF: The effects of tidal volume and end-expiratory pressure on pulmonary gas exchange during anesthesia. Anesthesiology 39:285-290, 1973
13. Meneely GR, Kaltreider NL: The volume of the lung determined by helium dilution: description of the method and comparison with other procedures. J Clin Invest 28:129-138, 1949
14. Needham CD, Rogan MC, McDonald I: Normal standards for lung volumes, intrapulmonary gas-mixing, and maximum breathing capacity. Thorax 9:313-325, 1954
15. Whitfield AGW, Waterhouse JAH, Arnott WM: Total lung volume and its subdivisions: study in physiological norms: basic data. Br J Soc Med 4:1-25, 1950
16. Kelman GR, Nunn JF: Nomograms for correction of blood Po_2, Pco_2, pH, and base excess for time and temperature. J Appl Physiol 21: 1484-1490, 1966
17. Riley RL, Lilienthal JL Jr, Proemmel DD, et al: On the determination of the physiologically effective pressures of oxygen and carbon dioxide in alveolar air. Am J Physiol 147:191-198, 1946
18. Finley TN, Lenfant C, Haab P, et al: Venous admixture in the pulmonary circulation of anesthetized dogs. J Appl Physiol 15: 418-424, 1960
19. Enghoff H: Volumen inefficax. Bemerkungen zur Frage des schädlichen Raumes. Upsala Lak Forhandl 44:191-218, 1938
20. Fowler WS: Lung function studies. II. The respiratory dead-space. Am J Physiol 154:405-416, 1948
21. Kuwabara S, Duncalf D: Effect of anatomic shunt on physiologic deadspace-to-tidal volume ratio: a new equation. Anesthesiology 31:575-577, 1969
22. Rattenborg C: Basic mechanics of artificial ventilation, Management of Life Threatening Poliomyelitis. Edited by HCA Lassen. London, E and S Livingstone, Ltd, 1956, p 23
23. Comroe JH Jr, Fowler WS: Lung function studies. VI. Detection of uneven alveolar ventilation during a single breath of oxygen. Am J Med 10:408-413, 1951
24. Comroe JH Jr, Forster RE, Dubois AB, et al: The Lung. Second edition. Chicago, Year Book Medical Publishers, 1962, pp 65-66
25. Snedecor GW, Cochran WG: Statistical Methods. Sixth edition. Ames, Iowa State University Press, 1967, pp 32-168
26. Lenfant C: Revival of an old battle: intermittent vs. continuous positive-pressure breathing. N Engl J Med 283:1463-1464, 1970
27. Asbaugh DG, Petty TL: Positive end-expiratory pressure: physiology, indications, and contraindications. J Thorac Cardiovasc Surg 65: 165-170, 1973
28. Agostini E, Mead J: Statics of the respiratory system, Handbook of Physiology, Section 3: Respiration. Vol 1. Edited by WO Fenn, H Rahn. Washington DC, American Physiological Society, 1964, pp 387-409
29. Young SL, Tierney DF, Clements JA: Mechanism of compliance change in excised rat lungs at low transpulmonary pressure. J Appl Physiol 29:780-785, 1970
30. Eckenhoff, JE, Enderby GEH, Larson A, et al: Pulmonary gas exchange during deliberate hypotension. Br J Anaesth 35:750-759, 1963
31. Shepard RH, Campbell EJM, Martin HB, et al: Factors affecting the pulmonary dead-space as determined by single breath analysis. J Appl Physiol 11:241-244, 1957