Relationships Between Lung Computed Tomographic Density, Gas Exchange, and PEEP in Acute Respiratory Failure

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Twenty-two patients with acute respiratory failure underwent lung computed tomography (CT) and physiological measurements at 5, 10, and 15 cm H2O positive end-expiratory pressure (PEEP) to investigate the relationship between morphology and function. Lung densities were primarily concentrated in the dependent regions. From the frequency distribution of CT numbers (difference in x-ray attenuation between water and lung) and lung gas volume measurements the authors obtained a quantitative estimate of normally inflated, poorly inflated, and non-inflated lung tissue weight. This estimated average lung weight was increased twofold above normal and excess lung weight correlated with the mean pulmonary artery pressure (P < 0.01). Venous admixture correlated with the non-inflated tissue mass (P < 0.01). Increasing PEEP caused progressive clearing of radiographic densities and increased the mass of normally inflated tissue (anatomic recruitment), while reducing venous admixture. The cardiac index decreased after increasing PEEP while oxygen delivery was unchanged. The authors conclude that CT scan lung density and oxygen exchange efficiency are correlated; the main effect of augmenting PEEP is to recruit perfused alveolar units that were previously collapsed. (Key words: Lung: acute respiratory failure; gas exchange. Measurement techniques: computer-assisted tomography. Ventilation: positive end-expiratory pressure.)

Since the introduction of positive end-expiratory pressure (PEEP) to treat acute respiratory failure due to diffuse lung parenchymal inflammation, several mechanisms have been postulated as responsible for alterations of gas exchange by augmented alveolar pressure. Among these, the most common hypotheses are recruitment of previously collapsed alveolar units and the reduction of cardiac output. Other possible mechanisms have been considered, such as diversion of pulmonary blood flow toward non-ventilated regions and/or the diversion of ventilation towards hypoventilated regions, overinflation of lung structures, and alterations of extravascular lung water and/or pulmonary blood volume. Most of these mechanisms have been inferred by measuring pulmonary mechanics, gas exchange, and hemodynamic modifications after applying several levels of PEEP.

In 22 patients with diffuse severe acute respiratory distress syndrome, we studied the morphological effects of varying PEEP levels on lung density as measured by computed tomography (CT).

A quantitative estimate of normally inflated, poorly inflated, and non-inflated lung tissue weight was obtained at different PEEP levels, and relationships between CT scan parameters and oxygen exchange efficiency were sought. We report here the correlations between morphology and function in these patients with acute respiratory failure (ARF), with particular emphasis upon the effects of PEEP.

Materials and Methods

STUDY PROCEDURE

Patient Population. Twenty-two consecutive patients with moderate to severe ARF/ARDS of varying etiology were included in this study. Patient selection into the study was based on the usual criteria of the adult respiratory distress syndrome: presence of hypoxemia, bilateral and diffuse opacities on the chest x-ray film, absence of left ventricular failure, and a recognized cause of increased pulmonary capillary permeability. Eight were females, 14 were males. The mean age was 39 ± 16 yr (SD). In ten patients, the ARF was due to pneumonia (four bacterial, six viral). In six, ARF followed severe trauma, while, in the remaining six patients, ARF originated from other causes (sepsis, pancreatitis, peritonitis, etc.). The trachea

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of each patient was intubated and the lungs of each patient were being mechanically ventilated. The elapsed time from tracheal intubation to the time of study averaged 99.6 ± 70 h (range 24–264 h). Sixteen of the 22 patients studied survived and were discharged.

Eight normal subjects (mean age 30 ± 4 y) without a history or physical exam suggesting lung disease were also studied with CT scanning to serve as a reference group.

Study Design. The study was conducted as part of a project for the study of ARF approved by the Human studies committee of Lombardia Region. Informed consent was obtained from the patients or relatives before study. All patients were sedated (morphine) and their muscles were paralyzed (pancuronium) throughout the procedure.

In the CT scan facility patients, vital signs were monitored with the same equipment used in the ICU. The patients’ lungs were ventilated with a Siemens (Stockholm, Sweden) Servo C ventilator with the following parameters: tidal volume = 10 ml·kg⁻¹, FIO₂ 0.6–1.0, depending on the venous admixture, a square pressure waveform, I/E ratio 1/1, and zero end-inspiratory pause. PEEP of 5, 10, and 15 cm H₂O was added while maintaining other ventilatory parameters constant; each level of PEEP was maintained for at least 25 min. After the end of each PEEP period, a CT scan was performed and respiratory, gas exchange, and hemodynamic variables were measured. The static volume/pressure (V/P) curve of the total respiratory system and the functional residual capacity (FRC) were determined in triplicate immediately before or after the CT scan study and the results were averaged.

CT Scan. We employed a Pfizer (Columbia, MD) ASE0450 CT scanner and exposures were taken at 120 KV, 50 mA, and 5 s. The slice thickness was 9 mm and the dimensions of the pixel of the reconstruction matrix were 1.5 × 1.5 mm. The system was calibrated with a suitable phantom. After obtaining a frontal scan covering the chest, we selected three levels of exposure: lung apex, hilum, and bases (above the diaphragm). Each exposure was obtained at end expiration with the selected PEEP level. Between each exposure, mechanical ventilation was resumed for about a minute. Each patient underwent three exposures at three levels of PEEP. No effort was made to correct for displacement of lung structures. Normal spontaneously breathing subjects underwent similar exposures during an end-expiratory pause (FRC) at atmospheric pressure (with the glottis open).

Physiological Data

Gas Exchange Parameters. All patients had intra-arterial catheters and 20 had Swan-Ganz thermodilution catheters. Blood samples (arterial and mixed venous) were collected at the end of each PEEP period, immediately before the CT scan. Samples were analyzed for pH, PO₂, PCO₂ (at 37°C), and hemoglobin and oxygen saturation. Expired gases were collected over a 5-min period in a Douglas bag at the same time as blood gas samples. Expired gas was analyzed for mixed expired CO₂ concentration, and the data were corrected for BTPS conditions.

The alveolar PO₂ (assuming an R = 1), the right-to-left venous admixture (Qsp/Qt), and the dead space fraction (Vd/Vt) were computed by standard formulae (at the FIO₂ in use); Vd/Vt was corrected for the effects of Qsp/Qt.

Hemodynamics. The arterial blood pressure (radial or dorsalis pedis) and pulmonary artery blood pressures (systolic, mean, diastolic, and wedge) were measured with transducers and recorded. In three patients, the pulmonary artery blood pressures in the CT scan facility were not recorded because of technical problems; this explains the discrepancy between the number of the patients studied and the number of data points in the figures of the Results section. The readings were taken at end expiration. Cardiac output was measured by thermodilution in triplicate and the results averaged. The cardiac index (CI) was computed. Oxygen delivery was computed as the product of arterial oxygen content and cardiac output.

Lung Mechanics. The volume/pressure curve (compliance) of the total respiratory system was measured using a large syringe (1500 ml capacity) through step-by-step inflation-deflation (100 ml at each step), after normalization of lung history, as previously described.

Functional residual capacity (FRC) was measured at atmospheric pressure by helium rebreathing, and the helium concentration was measured with a helium analyzer. Estimation of lung gas volume by dilution techniques does not allow the estimation of possible trapped gas, and if trapping occurs, the true lung gas volume results are underestimated. However, since helium dilution was obtained by providing large volume manual inflations gas trapping seems unlikely. Lung gas volumes at 5, 10, and 15 cm H₂O PEEP were derived by adding to the measured FRC the volumes computed on the inflation limb of the V/P curves to obtain 5, 10, and 15 cm H₂O pressures.

The ideal FRC (i.e., the FRC “expected” in subjects of the same sex and age, with respiratory paralysis and in a supine position) was computed according to Ibañez.

CT Scan Analysis

The CT scan analysis has been described elsewhere and will be summarized here. The quantitative analysis of CT scan data was based on the frequency distribution of the CT numbers. The CT number represents the linear attenuation coefficient of an x-ray in any given substance relative to the linear attenuation coefficient of water. In
our study conditions (constant incident energy, electron mass, lung tissue atomic number), the CT number and its variations are mainly related to physical density. When expressed in Hounsfield Units (H), the CT number is zero H for water, −1000 H for gas, and +1000 H for bone.

If we consider the lung as a mixture of water and gas (assuming that lung tissue has the density of water and including as lung “tissue” the lung’s structural components as well as blood and extravascular lung water), its average CT number is related to the relative proportion of gas and tissue by the following relationship:

\[
\text{Fraction of gas} = \frac{\text{CT}}{\text{CT gas} - \text{CT water}} \quad (1)
\]

where

\[
\text{Fraction of gas} = \frac{\text{Volume of gas}}{\text{volume of gas} + \text{volume of tissue}}
\]

This indicates, as an example, that if, in a given pixel, the CT number is −900 H, the fraction of gas will be 90%, while if the CT number is −800 H, the pixel is composed of 80% gas and 20% tissue.

\text{Estimate of Lung Weight. Actual lung weight:} Assuming that the three slices we obtained provide a representative sample of the entire lung, the average CT number of the total cross-sectional area (the sum of both apical, hilar, and basal sections) would then estimate the average CT number of the entire lung. Knowing the gas volume, which we measured with helium dilution and solving equation 1 for tissue volume, we could then estimate the lung’s weight, assuming that the specific weight of lung tissue is equal to 1 gm/cm³.

\text{Expected normal lung weight:} The expected normal weight of the lung, in a given patient, was estimated substituting the ideal FRC as the gas volume in equation 1, and employing, as an average CT number, an ‘ideal’ CT number of −670 H. The latter value is derived from the eight normal spontaneously breathing subjects. It is useful to note that the average CT number (−670 H), measured in normal subjects, had a small standard deviation (±10 H).

\text{Excess lung weight:} The excess lung weight was computed as the % ratio between the actual weight and the expected normal weight. For example, an excess weight of 100% indicates that the actual lung weight is twice the expected.

\text{Frequency Distribution of CT Number.} In every patient and, in any patient, for every level of PEEP, the CT frequency distribution was computed for 11 compartments (examining a 100 H segment for each compartment) from −1000 H to +100 H. Knowing the CT frequency distribution and the total lung volume (computed as the sum of the helium dilution gas volume and the tissue volume estimated by the average CT number of the entire lung [eq. 1]), it is possible to estimate lung weight for each radiodensity compartment. For example, if the frequency of CT number in the compartment −800 H is 30% and the total lung volume is 3000 ml (2000 ml gas volume, 1000 ml tissue volume), this compartment will have a volume of 900 ml, wherein 720 ml will be comprised of gas and 180 ml (i.e., 180 g) will be lung tissue.

\text{Estimate of the Weight of Normally Inflated, Poorly Inflated, and Non-inflated Lung Tissue.} To simplify the analysis of structure-function relationships, the eleven compartments were grouped into three compartments: normally inflated, poorly inflated, and non-inflated. These were defined by examining the frequency distribution of CT radiodensity of the normal subjects.\textsuperscript{11} We defined normally inflated as those compartments between −1000 H and −500 H; poorly inflated as those compartments between −500 H and −100 H; and non-inflated as those compartments between −100 H and +100 H; the weight of normally inflated, poorly inflated, and non-inflated lung tissue was then computed.

\text{An Analysis of Anatomic Gas Volume Recruitment.} The degree of anatomic recruitment was computed as the increase in weight of normally inflated tissue at 15 cm H₂O, the value normalized to expected normal lung weight. Ten percent anatomic recruitment when increasing from 5 to 15 cm H₂O PEEP would suggest that 10% of the original lung tissue (normally inflated), which consolidated during the disease process, was recruited at higher airway pressures from poorly or non-inflated compartments into the normally inflated compartment. We used weight instead of gas volume to estimate recruitment, because the increased weight of normally inflated tissue indicates new tissue was recruited to this compartment, independent of distension or overinflation of previously inflated units.

The increase of normally inflated tissue was normalized to the expected lung weight rather than to the actual weight of normally aerated tissue for the following reasons: if, in a patient, the quantity of normally inflated lung tissue increases from 50 g to 100 g, and the expected lung weight is 1000 g, then the anatomic recruitment will be computed as 5%. If, in another patient, normally inflated tissue increases from 200 g to 400 g, with the expected normal lung weight remaining 1000 g, anatomic recruitment will be 20%. If recruitment was not normalized, the first patient would have a similar recruitment fraction increase to that of the second patient, i.e., 100%, while the absolute anatomic incremental difference marked markedly differs. On the other hand, the absolute weight values cannot be used independently to portray increases of normally inflated lung tissue; for example, an identical 200 g increase may have a different effect in a patient where the
expected normal lung weight is 700 g compared with a patient where the expected normal lung weight is 1400 g.

STATISTICS

All data are expressed as mean ± SD. The least square method was used to perform a linear regression analysis. Student’s t test was used for comparison of the mean of paired samples. The Scheffe’ test was used for multiple comparisons.15 P < 0.05 was the accepted level for statistical significance.

Results

THE AVERAGE CT SCAN DENSITY AND ITS RELATIONSHIPS TO RESPIRATORY FUNCTION

Usually, in patients with ARDS, the lesions are distributed throughout the lungs in a nonhomogeneous manner.7,13,14†† Densities appear primarily in the dependent regions of the lungs, while non-dependent regions generally maintain a normal density. Figure 1, panel A, shows a typical CT distribution pattern of densities in a patient with ARF. The FRC, measured at zero cm H₂O end-expiratory pressure (ZEEP) in the 22 patients, averaged 1172 ± 552 ml (46% of their mean expected value), while the estimated lung weight was increased almost twofold above that expected (2590 ± 1200 g vs. 974 ± 220 g, P < 0.01). However, large variations of excess weight were measured. Some patients demonstrated minimal excess weight, while others had an excess weight increase of up to 400%. The excess weight of the lung in patients with

ARF averaged 184 ± 195%. The excess weight fraction correlated with mean pulmonary artery pressure, as shown in figure 2, as well as with both pulmonary diastolic pressure (r = 0.60, P < 0.01) and pulmonary wedge pressure (r = 0.48, P < 0.05).

In every patient, even those with the most severe ARF, some quantity of normally inflated tissue was present and was associated with a variable quantity of poorly and non-inflated tissue, as summarized in table 1 (normal patient values are added for comparison).

The impairment in gas exchange appears directly related to the quantity of non-inflated tissue. This is shown in figure 3, where PaO₂, Qsp/Qt, and VD/VT were correlated to the fraction of non-inflated tissue weight to actual lung weight. The data of figure 3 refer to measurements obtained at a 5 cm H₂O PEEP level; the same relationship, with the exception of VD/VT, existed at 10 and 15 cm H₂O PEEP.

Moreover, a close relationship between morphology and gas exchange is shown by other data derived from the CT scan: the average lung density (average CT number) and the absolute weight of non-inflated tissue were positively correlated with Qsp/Qt and negatively with PaO₂. On the other hand, the quantity of normally inflated tissue, as a fraction of total lung weight, correlated positively with the PaO₂ and negatively with Qsp/Qt at each level of PEEP. No correlation was found between the quantity of poorly aerated lung tissue and these gas exchange parameters.

**Table 1. Lung Density and Volume at Three Levels of Positive End-expiratory Pressure**

<table>
<thead>
<tr>
<th></th>
<th>Pts.</th>
<th>Normally Inflated Tissue (g)</th>
<th>Poorly Inflated Tissue (g)</th>
<th>Non-inflated Tissue (g)</th>
<th>Lung Weight (g)</th>
<th>Gas Volumes (ml)</th>
<th>Mean CT Numbers (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZEEP 0 cm H₂O</td>
<td>8</td>
<td>750 ± 170</td>
<td>155 ± 35</td>
<td>69 ± 18</td>
<td>974 ± 220</td>
<td>2562 ± 553</td>
<td>-670 ± 10</td>
</tr>
<tr>
<td>PEEP 5 cm H₂O</td>
<td>22</td>
<td>328 ± 170</td>
<td>574 ± 207</td>
<td>1687 ± 1134</td>
<td>2590 ± 1201</td>
<td>1173 ± 553</td>
<td>-324 ± 128</td>
</tr>
<tr>
<td>PEEP 10 cm H₂O</td>
<td>22</td>
<td>391 ± 210†</td>
<td>590 ± 232</td>
<td>1536 ± 99†</td>
<td>2318 ± 1160*</td>
<td>1416 ± 696†</td>
<td>-378 ± 129†</td>
</tr>
<tr>
<td>PEEP 15 cm H₂O</td>
<td>22</td>
<td>475 ± 210‡</td>
<td>590 ± 257</td>
<td>1073 ± 904‡</td>
<td>2138 ± 1107†</td>
<td>1597 ± 707*†</td>
<td>-441 ± 147†‡</td>
</tr>
</tbody>
</table>

* P < 0.05 vs. 5 PEEP.
† P < 0.01 vs. 5 PEEP.
‡ P < 0.01 vs. 10 PEEP.
FIG. 4. Frequency distribution of CT numbers in 11 compartments each comprising 100 Hounsfield Units (H) at 5 cm H$_2$O PEEP (white columns), at 10 cm H$_2$O PEEP (dashed columns), and 15 cm H$_2$O PEEP (black columns); normally inflated, poorly inflated, and non-inflated compartments are also indicated ($n = 22$).

**Effects of PEEP on Structure-Function Relationships**

Anatomic Gas Volume Recruitment. Characteristic morphological effects of PEEP on the lung are illustrated in figure 1, panel B. Augmenting PEEP usually induces substantial clearing of some lung regions of high density. This phenomenon can be analyzed in detail by measuring the variations of the CT frequency distribution at the different PEEP levels (fig. 4). Augmenting PEEP from 5 to 10 and 15 cm H$_2$O, the CT frequency appears to shift to the right in the normally inflated compartments (indicating an increase of frequency of pixels with normal gas/tissue ratios), while it shifts to the left in the non-inflated compartments (indicating a decrease in frequency of pixels with near zero gas/tissue ratios).

The quantitative variations with PEEP of normally inflated, poorly inflated, and non-inflated lung tissue weight are summarized in table 1. The quantity of normally inflated lung tissue increased significantly (alveolar recruitment), while the non-inflated tissue decreased ($P < 0.01$). No significant changes of the mass of poorly inflated tissue were observed when increasing PEEP. The increased PEEP was associated with a reduced total lung weight ($P < 0.01$; see table 1).

Alveolar Recruitment and Oxygen Exchange. Increased PEEP caused an overall improvement of oxygen exchange parameters, which are summarized in table 2. The gas exchange improvement parallels anatomic alveolar recruitment assessed by CT scan analysis, suggesting that recruited normally inflated tissue is perfused. The percent of anatomic recruitment (i.e., the difference between the normally inflated tissue weight at 15 and 5 cm H$_2$O PEEP normalized to the expected normal lung weight) correlated closely with the reduction of Qsp/Qt (fig. 5), as well as with the increase of Pao$_2$ ($r = 0.64$, $P < 0.01$). Conversely, the percentage reduction of non-inflated tissue was correlated with the decrease of Qsp/Qt ($r = 0.66$, $P < 0.01$) and the increase of Pao$_2$ ($r = 0.51$, $P < 0.05$).

**Table 2. Gas Exchange Parameters at Three Levels of Positive End-expiratory Pressure**

<table>
<thead>
<tr>
<th>PEEP 5 cm H$_2$O</th>
<th>PEEP 10 cm H$_2$O</th>
<th>PEEP 15 cm H$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pao$_2$ mmHg</td>
<td>Paco$_2$ mmHg</td>
<td>Qsp/Qt %</td>
</tr>
<tr>
<td>71.0 ± 29.5</td>
<td>39.8 ± 9.6</td>
<td>44 ± 18</td>
</tr>
<tr>
<td>93.5 ± 29.5†‡</td>
<td>38.0 ± 8.2*</td>
<td>36.5 ± 15*</td>
</tr>
<tr>
<td>93.5 ± 29.5†‡</td>
<td>28 ± 12 †‡</td>
<td>59 ± 14</td>
</tr>
<tr>
<td>100 ± 380</td>
<td>70.5 ± 8.1‡</td>
<td>67.4 ± 10.7‡</td>
</tr>
<tr>
<td>4.69 ± 1.50</td>
<td>3.97 ± 1.18†</td>
<td>4.25 ± 1.39*</td>
</tr>
</tbody>
</table>

Pao$_2$ = arterial Pao$_2$; Paco$_2$ = arterial Paco$_2$; Qsp/Qt = right to left shunt fraction; VD/VT = dead space fraction; oxygen delivery = O$_2$ arterial content multiplied by cardiac output; Sat O$_2$ = hemoglobin oxygen saturation of mixed venous blood.

* $P < 0.05$ vs. 5 PEEP.
† $P < 0.01$ vs. 5 PEEP.
‡ $P < 0.01$ vs. 10 PEEP.
of CI was associated with the decreased Qsp/Qt (r = 0.53, P < 0.01).

Overinflation of Lung Structures. Overinflation is indicated by an abnormal increase of the gas/tissue ratio. The lung regions with the highest gas/tissue ratio are grouped in the compartment between −1000 H and −900 H. The CT frequency, in this compartment, increased significantly with PEEP from 0.57 ± 0.65% to 3.10 ± 4.01% (P < 0.05; see fig. 4). However, the latter values are similar to those observed in normal subjects (2.14 ± 3%) breathing at atmospheric pressure.

Discussion

CT Scan Anatomy and Function

The CT scanning morphology of lung in patients with ARF as determined by CT scanning appeared consistent with previous reports, dense lesions concentrated in the dependent regions of both lungs. Gravity thus plays an important role. The same, although quantitatively smaller, phenomenon was observed in normal subjects during paralysis and anesthesia, and was primarily attributed to lung compression and atelectasis. The CT area of densities reported in normal subjects, during anesthesia and paralysis, averaged 8–10% of the total lung field, while the density area we measured in patients with ARF was five to eight times greater.

Compression atelectasis is probably not the only phenomenon occurring in patients with ARF. Unfortunately, the densities detected by CT scanning cannot be separated into atelectasis, edema, consolidation, or blood pooling. However, the total weight of the lung (and, consequently, the total amount of intra- and extra-vascular lung water) may be inferred from the CT numbers and gas volume measurements.

The computation of lung weight, as derived here, assumes that the three levels of the CT scan provide a representative sample of the entire lung at whatever PEEP level is being used. In the isolated lung of normal animals, we found that the difference between the weight computed by CT scan and gas volume at different inflation pressures and the directly measured lung weight was approximately 2%. In patients with ARF, we have no direct proof that the three slices provide a representative sample of the lung. However, the weights we computed agree with the weight ranges of lungs measured at autopsy of patients with ARF. Moreover, the CT scan computed weight of lungs in normal subjects appears in the same range as the weights of histologically normal lungs at autopsy.

The lung weight increase of patients with ARF was expressed as "excess weight" and was, on average, 18% of the expected normal weight. These values markedly exceed the average increase of extravascular lung water reported in patients with ARF. However, it is important to recall that the double indicator dilution technique only estimates extravascular water in lung regions that are perfused with flowing blood, while the CT scan estimate of lung weight is independent of perfusion.

A good correlation was observed between mean pulmonary artery pressure and the excess weight of the lung. The same relationship was observed by several authors in experimental settings. It is tempting to speculate that the increased mean pulmonary artery pressure is responsible for the increased weight in an injured lung. On the other hand, it is possible that extravascular lung engorgement, via "weight mediated" vascular compression, may induce a further increase of pulmonary artery pressure. This may create a sort of vicious circle leading to increasing edema and pulmonary hypertension. Whatever the various causes and cofactors involved in the pathogenesis of inflammatory pulmonary edema, the densities appear unevenly distributed throughout the lung and localized, preferentially, in dependent regions. Each patient, to a variable degree, showed regions of normal density (usually superior) associated with regions of increased density and regions where little or no gas was present.

By using the CT frequency distribution, we attempted to quantitate these regions and separate them into normally inflated, poorly inflated, and non-inflated tissue compartments. Two of these compartments, the normally
inflated and the non-inflated, appear importantly related to gas exchange, while the poorly inflated compartment appeared independent of gas exchange.

The oxygenation abnormalities were correlated with the quantity of non-inflated tissue. This suggests that the perfusion of non-inflated tissue, measured as $Q_{sp}/Q_{t}$, is, in fact, the main cause of hypoxemia in patients with ARF, since $VA/Q$ mismatch is usually negligible, particularly in the range of $F_{1}O_{2}$ (0.6–1) our patients required to prevent hypoxemia.28

**Structure-function Effects of PEEP**

Increasing the PEEP by 5 and 10 cm H$_{2}$O caused, on average, a variable reduction of radiographic densities. These reductions occur rapidly (less than 30 min) and are reflected by an altered distribution of the CT number frequency.

By increasing PEEP, we found a significant decrease in lung weight of approximately 200 g for every additional 5 cm H$_{2}$O PEEP. This may be due both to a decrease of lung blood volume and/or of extravascular lung water. However, while Thorvaldston et al.29 actually showed a decrease in lung blood volume when increasing PEEP, it has been shown3 that PEEP does not decrease the volume of extravascular lung water. Unfortunately, with the method we used, we cannot discriminate between these two factors. On the other hand, we may not exclude a systematic underestimation of lung weight when increasing PEEP levels. The lung gas volumes were computed by adding to the FRC value measured at ZEEP, the gas volumes needed to reach the PEEP pressure on the inflation limb of the V/P curve. This may underestimate the lung gas volume, and, hence, underestimate the lung weight, since, at any measured CT number, the lung weight is proportional to the gas volume (see eq. 1). However, a systematic underestimation of lung weight, if any, would increase the significance of increases of the weight of the normally inflated compartment at higher PEEP levels.

Increasing PEEP from 5 to 15 cm H$_{2}$O was associated with three phenomena: normally inflated tissue mass increased an average 15%; $Q_{sp}/Q_{t}$ decreased 16%; and CI decreased 15%. The increase of the normally inflated tissue mass is a quantitative estimate of the real alveolar recruitment, independent of alveolar distension or overinflation. An increase of inflation of pulmonary units already inflated (i.e., alveolar distension or overinflation without recruitment) would only decrease the CT number in the range between −500 H to −1000 H, without affecting the computed weight of this compartment, which remains unmodified (see eq. 1). Within the normally inflated compartment (−500 H to −1000 H), overinflation may be assessed by a change in CT number frequency of the compartment with the highest gas/tissue ratio (−900 H to −1000 H). This compartment has been found to be over-represented in subjects with emphysema.18 The overinflation measured at 15 cm H$_{2}$O PEEP (the highest level of pressure at which the CT scanning was performed) is quantitatively small (2–4% of the entire lung). This does not exclude a possible significant overinflation at peak ventilator pressure. Alveolar gas recruitment, as assessed by the CT scan and compliance measurements, is "anatomic," indicating the appearance of new pulmonary units with normal gas/tissue ratio. While anatomic recruitment increases lung compliance7,36 to improve oxygen exchange, it is necessary that the recruited units be perfused and collapsed before recruitment, and then maintain perfusion after inflation at increasing PEEP. In this study, we found that anatomic recruitment, as assessed by the CT scan, was closely associated with decreasing $Q_{sp}/Q_{t}$, suggesting that the recruited gas exchange units were perfused both before and after the PEEP increase, i.e., "anatomic recruitment" parallels "functional recruitment."

The decreasing $Q_{sp}/Q_{t}$ as PEEP increased was also associated with a decreased CI. There are many reports of a positive correlation between CI and $Q_{sp}/Q_{t}$ in patients with ARF,31,38 and it has been suggested that a major effect of PEEP on gas exchange is related to the decreased CI.3 Unfortunately, the precise relationships between CI, alveolar recruitment, and $Q_{sp}/Q_{t}$ changes with PEEP (15–16% in our patients) is uncertain, and only hypotheses may be advanced. If the $Q_{sp}/Q_{t}$ reduction induced by PEEP is primarily due to the concomitant reduction of CI, this implies that progressively smaller fractions of pulmonary blood flow are distributed to non-inflated tissue when CI decreases, via an unknown mechanism.

We propose an alternative hypothesis for the CI-$Q_{sp}/Q_{t}$ relationship, wherein the independent variable is not CI but $Q_{sp}/Q_{t}$. An elevated CI is a common finding often associated with sepsis and hypoxemia in previously healthy patients with ARF. If PEEP augments arterial oxygenation by recruiting newly inflated and perfused gas exchange units, the CI decrease may simply reflect a CI return toward more normal values. The adequacy of the "reduced" CI to provide an adequate oxygen supply, in the patients with ARF we studied, is evidenced by the unchanged mixed venous oxygen saturation and systemic oxygen delivery at 15 cm H$_{2}$O PEEP (table 2). This does not exclude having $Q_{sp}/Q_{t}$ as the dependent variable of CI when the latter is "artificially" modified by drugs that alter the pulmonary vascular tone,31,32 or if CI is sufficiently reduced to significantly decrease mixed venous oxygen saturation.33

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