Pulmonary perfusion in supine and prone positions: an electron-beam computed tomography study

ANDREW T. JONES, DAVID M. HANSELL, AND TIMOTHY W. EVANS

1Unit of Critical Care and 2Department of Imaging, National Heart and Lung Institute, Imperial College School of Medicine, Royal Brompton Hospital, London SW3 6NP, United Kingdom

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Jones, Andrew T., David M. Hansell, and Timothy W. Evans. Pulmonary perfusion in supine and prone positions: an electron-beam computed tomography study. J Appl Physiol 90: 1342–1348, 2001.—Acute respiratory distress syndrome is characterized by alterations in the ventilation-perfusion ratio. Present techniques for studying regional pulmonary perfusion are difficult to apply in the critically ill. Electron-beam computed tomography was used to study the effects of prone positioning on regional pulmonary perfusion in six healthy subjects. Contrast-enhanced sections were obtained sequentially in the supine, prone, and (original) supine positions at full inspiration. Regions of interest were placed along the nondependent to dependent axis and relative perfusion calculated. When corrected for the redistribution of lung parenchyma, a gravitational gradient of pulmonary perfusion existed in both supine and prone positions. The distribution of perfusion between the supine or prone positions did not differ, but data analysis using smaller regions of interest demonstrated marked heterogeneity of perfusion between anatomically adjacent regions of lung. The distribution of lung parenchyma was more uniform in the prone position. Gravity was estimated to be responsible for 22–34% of perfusion heterogeneity in the supine and 27–41% in the prone positions. These data support the hypothesis that factors other than gravity may be at least as important in determining the distribution of pulmonary perfusion in humans. The influence of nongravitational factors may not be detectable if techniques that sample large tissue volumes are employed.

METHODS

The first aim of the present study was therefore to characterize the distribution of regional pulmonary perfusion in healthy human subjects, in both supine and prone positions, during the application of positive-pressure ventilation using EBCT. Second, to address issues concerning the influence of spatial resolution, data were analyzed by use of regions of interest (ROI) of differing size.

The protocol for these investigations was approved by the Ethics Committee of the Royal Brompton Hospital, and informed consent was obtained from all participants. In all studies, subjects were placed in the supine position within the computerized tomography (CT) scanner (Imatron C150L, Imatron, San Francisco, CA) and established on intermittent positive-pressure ventilation administered via a mouthpiece (Evita II, Drager, Lubeck, Germany), using an inspired oxygen concentration of 0.21 and tidal volume (VT) of 10–12 ml/kg.

CT scanning protocol. For the purpose of constructing time-density curves, a rapid multissection scan acquisition was performed at a single level, immediately before and after the rapid, automated injection (60 ml at 20 ml/s; Angiomat
6000, Liebal-Flarsheim, UK) of radiopaque contrast material (Omnipaque 300 iodine mg/ml, Nycomed, Amersham, UK), via a 16-gauge cannula placed in an antecubital fossa vein. Fifteen to twenty 6-mm sections were obtained in each study. The acquisition time for each section was 100 ms. The interval between the acquisition of each image was designed to allow construction of complete time-density curves for the lung parenchyma and left-sided circulation (descending aorta). The scans were electrocardiogram gated, and each series was performed during an inspiratory breath-holding maneuver.

After commencement of positive-pressure ventilation, each subject was left for 15 min to achieve a steady state, after which a multisection scan was obtained at a level 2–3 cm above the right hemidiaphragm. On completion, the subject’s position was marked externally with a laser alignment device. The subject was then returned to the supine position, and, after an identical 15-min stabilization period, a second multisection scan was performed at the same level. The subject was then turned into the prone position, and, after an identical 15-min stabilization period, a second multisection scan was performed at the same level. The subject was then returned to the supine position, aligned as for the first scan, and a final multisection scan was obtained after a further 15 min. Comparable positioning of the prone and second supine scans was additionally confirmed by matching of the pulmonary branching pattern. During each inspiratory breath-hold maneuver, the plateau pressure and VT were noted from the ventilator display.

Calculation of perfusion using EBCT. By using EBCT and following the Sapirstein principle (33), perfusion can be calculated by using equations derived from conventional microsphere approaches to blood flow analysis (8, 9, 32, 37)

$$\frac{\text{PBF/V}}{\text{CT ROI} - \text{CT air}} = \frac{\Delta \text{Pul}}{\int C_{DA} \, dt}$$

where $\text{PBF/V}$ is blood flow per unit volume of lung, $\Delta \text{Pul}$ is the peak Hounsfield unit (HU) change due to contrast material, and $\int C_{DA} \, dt$ is the area under the time-density curve for the descending aorta by a gamma variate fit.

To express blood flow per unit volume of lung parenchyma, it is assumed that the ROI is composed of air and “water” (i.e., blood and parenchyma). The disparate densities of these components allow the fraction of each to be calculated by using the CT gray scale or Hounsfield number for any ROI. For example, the water fraction can be calculated by subtracting the CT value of pure air from the mean CT value of an ROI to give a value reflecting the amount (density) of parenchyma and blood present in the selected region. Comparing this value to the continuum ranging from water (0 HU) to air (1,000 HU) allows the percentage of the ROI that is water (blood and parenchyma) to be calculated thus (34)

$$\frac{\text{CT ROI} - \text{CT air}}{\text{CT blood} - \text{CT air}}$$

The air fraction of an ROI, is simply $1 - \text{“water”}$ fraction. Furthermore, the amount of blood present within an ROI can be computed by comparing the time-density curve of the ROI to that of the feeding/draining vessel

$$\text{Blood} = \frac{\int \text{ROI}(t) \, dt}{\int \text{DA}(t) \, dt}$$

Subtracting the result from the water fraction produces the percentage of the ROI that is lung parenchyma. Blood flow per unit volume of lung parenchyma can then be calculated by dividing the absolute blood flow per milliliter of lung tissue (blood, parenchyma, and air) by the fraction of parenchyma in the ROI.

Image analysis. The images obtained were viewed on an off-line workstation and analyzed by use of the scanner’s proprietary software (version 12.4, Imatron, San Francisco, CA). ROI were placed in five regions, at 10, 30, 50, 70 and 90% of the dependent-nondependent lung distance, and time-density curves were constructed for each ROI by using a gamma-variate fit to exclude recirculation. Two approaches were used to calculate perfusion in each sample region: first, a single ROI (ROI$_S$) with an approximate sample area of 7–10 cm$^2$ (volume 4–6 cm$^3$) and, second, multiple smaller ROI (ROI$_M$) with an approximate sample area of 1 cm$^2$ (volume 0.6 cm$^3$), aiming to avoid all pulmonary vessels (Fig. 1).

Fig. 1. Image analysis. Regions of interest (ROI) were placed at 10, 30, 50, 70, and 90% of vertical lung height. A: single ROI (ROI$_S$) supine. B: ROI$_S$ prone. C: multiple ROI (ROI$_M$) supine, examining perfusion at ~10% of the vertical lung height. A typical time-density curve is illustrated in each case.
1). In both cases, perfusion was calculated by using the technique previously outlined and was expressed as a fraction of the mean perfusion of the given section. The mean perfusion was obtained from an ROI that outlined the whole of the lung section, excluding the hilar and central vessels.

**Statistical analysis.** Comparisons between ventilatory parameters during each intervention and differences in regional perfusion (ROI\(_S\)) under the same study conditions were made by using analyses of variance (Prism v3.1, Graphpad, San Diego, CA). For comparisons of perfusion distributions (ROI\(_M\)) under different study conditions, a two-way analysis of variance was applied. For comparison of perfusion gradients using both ROI\(_S\) and ROI\(_M\), linear regression analysis was applied. The coefficient of correlation used to quantify the strength of any linear relationship observed, and the square of the coefficient of correlation was used to quantify the proportion of flow variability explicable by the independent variable. A P value of \(p \leq 0.05\) was considered statistically significant.

**RESULTS**

Six healthy, nonsmoking male subjects (age range 23–44 yr) were studied. All tolerated the procedure without difficulty or adverse effects. During the course of the study, there was a small but statistically significant increase in VT (from 0.89 ± 0.01 to 0.98 ± 0.04 liters; \(P = 0.05\)) but no difference in plateau pressure (\(P > 0.05\)) (Table 1). In one subject, it was not possible using ROI\(_S\) to estimate accurately the area under the time-density curve for the lung and therefore corrected perfusion values, and tissue composition data were impossible to obtain.

With the use of ROI\(_S\) to examine uncorrected perfusion, a nondependent-to-dependent gradient was apparent in both supine and prone positions (\(P < 0.01\), Fig. 2). There was no difference in the distribution of perfusion between the two supine scans (data not shown, \(P > 0.05\)) nor between the relative perfusion values in either position (\(P = 0.91\), Fig. 2). Although the gradient of perfusion was less in the prone position, this failed to reach statistical significance (\(-1.30\ vs. \(-1.02\)% mean perfusion/% height of lung section, supine vs. prone; \(P = 0.15\), Fig. 2).

With the use of ROI\(_M\) to examine uncorrected perfusion, the variation in perfusion values in anatomically adjacent regions was marked (Fig. 2). A nondependent-to-dependent gradient was apparent in both positions (\(r^2 = 0.74\) supine; \(r^2 = 0.68\); \(P < 0.01\)) but was more uniform in the prone position with evidence of redistribution of perfusion to nondependent regions (\(-1.15\ vs. \(-0.94\)% mean perfusion/% height of lung section, supine vs. prone; \(P < 0.001\)).

**Table 1. Ventilator recordings, Pplat, and VT during first supine, prone, and second supine scans in subjects undergoing the repositioning protocol**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supine 1</th>
<th>Prone</th>
<th>Supine 2</th>
<th>(P) (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pplat, cmH(_2)O</td>
<td>9.5 ± 1.3</td>
<td>11.2 ± 1.5</td>
<td>11.5 ± 0.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VT, liters</td>
<td>0.89 ± 0.01</td>
<td>0.92 ± 0.03</td>
<td>0.98 ± 0.04</td>
<td>=0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE. Supine 1 and supine 2, first and second supine scans, respectively; Pplat, plateau pressure; VT, tidal volume.

When perfusion (ROI\(_S\), ROI\(_M\)) was corrected for the volume of lung parenchyma (Fig. 3), the gravitational gradient persisted with the use of both methods of analysis in both positions, although it was reduced. When ROI\(_S\) was used, there was no significant difference in the distribution of perfusion between the two supine scans (data not shown \(P > 0.05\)) nor between supine and prone positions (\(P > 0.24\)). When ROI\(_M\) analysis was used, the relationship between nondependent/dependent position and relative perfusion was weaker than that seen for uncorrected perfusion values (\(r^2 = 0.22\) supine; \(r^2 = 0.28\) prone; \(P < 0.01\)). The data also revealed decreased perfusion in the lowest regions
of the lung section. In such areas, it has been shown that other factors, such as differences in alveolar ventilation and increased tissue pressure, may exert an additional effect on pulmonary perfusion. Thus excluding data from the lowest 20% of the lung section strengthened the relationship between nondependent/dependent position and relative perfusion ($r^2 = 0.34$ supine, $r^2 = 0.41$ prone; $P < 0.01$). With either means of analysis, there was no difference in the gradient of the perfusion distributions in either position ($P = 0.81–0.98$).

When using ROI$_S$, there was an increase in lung parenchyma per unit volume of tissue in the supine position moving from nondependent to dependent lung regions ($P < 0.01$) (Fig. 4). By contrast, no such gradient was seen in the prone position, the distribution of lung parenchyma being uniform across the lung section ($P > 0.74$). When ROI$_M$ was used, a vertical gradient in lung parenchyma per unit volume of tissue was observed in both supine and prone positions ($P < 0.01$). In the prone position, the gradient of the distribution was less pronounced ($P < 0.01$) (Fig. 4). Tissue composition data (ROI$_S$) are not shown but are available from the authors by request.

**DISCUSSION**

Changing ventilation-perfusion relationships through prone positioning has assumed increasing therapeutic significance in critically ill patients with lung injury requiring mechanical ventilation. EBCT can quantify pulmonary blood flow and may provide further insights into this physiological response. To our knowledge, this study is the first to employ this approach to investigate regional pulmonary perfusion in human subjects, mechanically ventilated to reproduce the effects of ventilatory support applied to critically ill patients.

In the present study, we have demonstrated a vertical gradient of perfusion that persists in the supine and prone positions. This might be predicted in that lung tissue is compressible, leading to a greater tissue density in dependent regions. However, the preservation of this gradient after volume correction suggests the existence of a true gravitational effect in both positions. Our data also suggest that, in the prone position, uncorrected perfusion was slightly increased in nondependent regions. However, this less steep gradient did not persist when perfusion was corrected for tissue volume, suggesting that it is attributable to the redistribution of lung tissue. Indeed, in this study, the
distribution of lung parenchyma was more uniform in the prone position. Although not a direct measure of regional ventilation, because studies were timed to end-inspiration, the more uniform distribution of parenchyma supports the concept of a more even distribution of ventilation in the prone position (19, 20, 29).

Second, we aimed to investigate the influence of spatial resolution by analyzing data using ROI of differing sizes. Although higher resolution sampling did not significantly alter the distribution of perfusion observed in either position, it gives much clearer insights into the degree of perfusion heterogeneity within the lung and raises the possibility that factors other than gravity may be equally or more important in determining the distribution of pulmonary perfusion. The influence of gravity on the distribution of pulmonary perfusion has been traditionally explained by the interrelationships among alveolar, pulmonary arterial and venous, and interstitial pressures (15, 35, 36). The gravitational distribution has since been demonstrated in all postures, although it may be less pronounced in the prone position (10, 31). Recent studies in animals using injected microspheres and high-spatial-resolution techniques have suggested that the branching pattern of the pulmonary vascular tree leads to more heterogeneity of perfusion than could be explained by gravity alone, the so-called fractal hypothesis (5, 6). Gravity was found to account for only 2–10% of the perfusion heterogeneity in the prone and supine postures in dogs (6) but up to 27% in upright baboons (5). In experimental dogs, blood flow remained preferentially distributed to nondependent dorsal regions when prone (6).

Our results are both in agreement and at variance with these studies. Using ROI_m, we found high levels of perfusion heterogeneity throughout the lung section. Moreover, in the present study, gravity accounted for 22–31% and 27–41% of perfusion heterogeneity in the supine and prone positions, respectively. These findings are comparable to those described in recent animal studies, although the effect of gravity is seemingly slightly greater in humans. In support of our findings, studies performed during spaceflight reveal that the distribution of pulmonary blood flow is more uniform under conditions of microgravity (30), suggesting that gravity does indeed play a role in the distribution of perfusion in humans under normal conditions.

By contrast, several factors could explain the differences between our data and these recent animal studies. First, it has been suggested that, in quadrupeds, gravity may not be as important a determinant of regional pulmonary blood flow because of their relatively smaller lung volumes (14, 15). Second, the pulmonary vasculature of most laboratory animals is more muscularized, with a different distribution of vascular resistance. In humans (as well as other primates), a smaller fraction of vascular resistance resides in the microvasculature; therefore, the gravitational effects of hydrostatic pressure may be more marked (14). Third, the application of positive-pressure ventilation accentuates the normal ventral-dorsal gradient of pulmonary perfusion in the supine position (11, 12, 15, 18) and could partly explain the more prominent gravitational gradient observed in our study. Finally, differences in animal size, and therefore vertical gravitational gradient, may also have an effect.

Technical considerations may interfere with the ability of EBCT to measure regional pulmonary perfusion. Both experimental (16, 24) and clinical (2, 9, 17, 23, 32)
studies indicate a correlation between EBCT-generated measures of perfusion and “true” perfusion values derived from conventional techniques. However, EBCT measures of perfusion may underestimate true perfusion, principally because of early washout of contrast from the ROI. This effect is most pronounced at higher flow rates, so it is possible that our results represent an underestimation of the true gravitational gradient. Second, unlike mechanical CT scanners, the X-ray source of the EBCT does not rotate about the scanned object through a full 360° (26). Consequently, irradiation of the patient, scatter, and noise distribution are radially asymmetrical. In the present study, the descending aorta was used as the reference when calculating pulmonary perfusion. In the prone position, the nondependent descending aorta lies in a region of higher exposure variability. Furthermore, in the prone position, beam hardening from contrast-enhanced intracardiac blood interposed between the beam and descending aorta may affect density values (4). However, if such considerations are valid, reference values in the prone position should have been consistently less than those for the supine scans. This was not the case after analysis of curves from individual subjects. Third, radiographic contrast agents may influence vascular tone (13, 25, 28). However, we identified no difference in the distribution of perfusion nor between the reference values when comparing the two supine scans, arguing against a significant vasodilator effect due to contrast.

The degree of random noise inherent in our data and its possible effect on our estimations of a gravitational effect are more difficult to calculate. Our data do not represent repeated measures; therefore, accurate estimates of random noise are not possible. EBCT measures of parenchymal density encountered during this study ranged between −600 and −950 HU, and the standard deviation for the given values within this range was ±5–10 HU. Although we express the degree of perfusion heterogeneity due to gravitational forces estimated by our data as between (at least) 22 and (at most) 41%, depending on the position and region of the lung section examined, this leaves 59–78% of perfusion heterogeneity to be explained by other factors. These include the structure of the pulmonary vascular tree, effects of positive-pressure ventilation, regional changes in local alveolar pressures, and differences in cardiac output between subjects, as well as the effect of random noise. However, we suggest it to be unrealistic to attempt to apportion the amount of this unexplained range that is due to random noise, because the wide differences in levels of perfusion within the lung section would cause any estimates for coefficients of variation for the data to vary, depending on the region examined.

In summary, we have shown that the regional distribution of pulmonary perfusion may be quantified in human subjects by using EBCT. Our findings concur with recent animal studies that suggest that there is a large degree of perfusion heterogeneity with the lung, which is only partly explained by the effects of gravity.

The influence of nongravitational factors, which include the anatomical arrangement of the pulmonary vasculature tree, may not be accurately identified when techniques that use larger ROI are employed.

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REFERENCES


