Regional differences in gas exchange in the lung of erect man

J. B. WEST
Department of Physiology, The University of Buffalo School of Medicine, Buffalo, New York

Measurements of regional ventilation and blood flow using radioactive CO₂ show that both increase from apex to base of the lung; the results are used to build an integrated picture of gas exchange. Ventilation-perfusion ratios at nine levels of the lung have been calculated and differences in local gas exchange deduced. In the resulting model, alveolar O₂ tension changes by more than 40 mm Hg from apex to base while CO₂ and N₂ tensions change by about 14 and 29 mm Hg, respectively. Maximal differences in O₂ saturation of end-capillary blood are 4% but differences in CO₂ contents of 7 vol% and pH variations of 0.12 units occur. The O₂ uptake per unit lung volume increases eightfold down the lung while corresponding variations in CO₂ output are less than threefold. N₂ passes out of the blood in upper parts of the lung but into the blood in basal regions (net exchange is zero). Over-all O₂ uptake and CO₂ outputs are reduced by only 2–3% by the ventilation-perfusion ratio inequality, causing alveolar-arterial differences of 4, 1, and 3 mm Hg for O₂, CO₂, and N₂, respectively.

JOHANNES ORTH (1) suggested, in 1887, that anemia would develop in the apex of the upright lung more easily than in other parts because of the weight of the column of pulmonary blood, and since then, much evidence has accumulated to show that the blood flow to the upper parts of the erect lung is less than to the lower regions. For example, Martin and his colleagues (2) showed that the respiratory exchange ratio was higher in the upper lobes than in the lower; Mattson and Carlens (3) measured a low oxygen uptake in the right upper lobe compared with the rest of the right lung, and Rahn et al. (4) found a higher ventilation-perfusion ratio in the uppermost lobe of the dog lung than would be predicted from its ventilation. All these findings suggest that the upper lobes are poorly perfused.

With the introduction of radioactive gases which could be detected inside the lung by external counting over the chest wall, more precise measurements of regional blood flow and ventilation became possible. Knipping and his colleagues (5) used xenon 133 to localize areas of defective ventilation in patients with lung disease. Oxygen 15 is more versatile. Not only can the distribution of the inhaled gas be measured by counters over the chest, but information about regional gas exchange can be obtained by recording the rate of removal of the gas during a short breath-holding period. This has been done using oxygen, carbon monoxide, carbon dioxide, and water vapor, all labeled with oxygen 15. Of these gases, radioactive carbon dioxide has been preferred for the measurements of regional pulmonary blood flow. Recently a new technique for measuring perfusion with xenon 133 has also been described (6).

Oxygen 15 has a half-life of 2 min; it was prepared on the Medical Research Council cyclotron in the grounds of Hammersmith Hospital (7). The subject took a breath of labeled carbon dioxide and held his breath for about 10 sec. Counters aligned in front of and behind the chest detected the radioactive gas within an anteroposterior core of lung tissue. The counting rate at the end of inspiration was determined by the ventilation and volume of the lung in the counting field, and the rate at which the counting rate falls (clearance rate) during the short breath-holding period was taken as a measure of the regional blood flow.

On the basis of measurements previously reported (8), the relative ventilation-perfusion ratios in nine horizontal sections of the normal erect lung can be calculated. With this information, it is possible to predict the complete local gas exchange in each section and also the over-all gas exchange as usually measured, including the alveolar-arterial gas differences resulting from the uneven distribution of blood and gas. This study is therefore an attempt to describe in detail the variations in local gas exchange of the human lung in the erect posture. Although certain assumptions are necessary, it may serve as a preliminary model until more precise data can be obtained.

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flow) increased as the counters were moved down the chest. In Fig. 1, the original clearance rate data (8) have been replotted with the results from both lungs pooled, except for the lowest three counting positions on the left side where labeled blood in the heart interfered with the measurement. A straight line was drawn through the plot of clearance rate against anterior rib marking, and this showed a ninefold difference between the levels of the first and fifth intercostal spaces. In Fig. 2 an over-all cardiac output of 6 liters/min has been assumed and the blood flow expressed in liters per minute per cent lung volume, values of 0.011 and 0.099 liter/min % lung volume being obtained for the uppermost and lowermost regions, respectively. Table 1 shows the figures from which these values were derived. The increase in clearance rate was found to be approximately linear with distance down the chest. The difference between upper and lower zones was abolished when the subjects lay supine; on moderate exercise, the clearance rate of the upper zone increased more than the lower so that the inequality was reduced (8). Clearance rates at the same horizontal level across one lung in the upright position showed no consistent differences.

Differences in regional ventilation per unit lung volume were also detected but these were much less marked than the variations in blood flow. Thus the ventilations at the levels of the second intercostal space and the fifth rib anteriorly were in the ratio of 1.4:1. Again, by taking an over-all alveolar ventilation of 5.1 liters/min (corresponding to an over-all ventilation-perfusion ratio of 0.85), the ventilation can be expressed in liters per minute per cent lung volume. The present series of measurements did not give any information on how the ventilation changed between the upper and lower lung zones. However, Ball and his co-workers (6) found an approximately linear increase in ventilation per unit lung volume, and if this distribution pattern is used here, values of 0.04 and 0.06 liter/min % lung volume are obtained for the uppermost and lowermost regions, respectively. Because the blood flow increased more rapidly than the ventilation down the lung, there was a progressive fall in ventilation-perfusion ratio of 3.3:0.63 from the apex to the base (Fig. 2).

**CONSEQUENCES OF DISTRIBUTION OF PERFUSION AND VENTILATION**

The gas exchange which occurs in any part of the lung is determined by the ventilation-perfusion ratio, in the absence of diffusion limitations. Thus the measured distributions of perfusion and ventilation can be used to depict the pattern of gas exchange throughout the whole lung. To construct the model, the lung was divided into nine imaginary horizontal slices corresponding to the nine counting positions used, and from measurements on cadavers the volume of lung in each slice was determined (8). A cardiac output of 6 liters/min, an over-all ventilation-perfusion ratio of 0.85, and O2 and CO2 tensions of 40 and 45 mm Hg, respectively, in mixed venous blood were assumed. With the blood flow and ventilation data, the position of each lung slice on an O2-CO2 diagram could then be fixed (Fig. 3) and much information about its gas exchange deduced.

It can be seen from Table 1 that not all the lung is covered by the nine slices because the extreme apex and the regions in the costophrenic angles could not be included in the counting fields without large errors being made. The volume of the lower regions, which was excluded, is exaggerated in Table 1 because, in fact, the diaphragm is dome-shaped with the lung tissue forming a

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**Fig. 1.** Clearance rate of radioactive carbon dioxide plotted against the counter position (referred to the anterior ribs). Data from 16 normal subjects (8); means and se. Measurements from both lungs are pooled except for those from lowest 3 positions on left side where labeled blood in the heart caused interference.

**Fig. 2.** Changes in blood flow (Q) and ventilation (VA) per unit lung volume, down the lung (right-hand scale). Resultant ventilation-perfusion ratio (VA/Q) is also shown (left-hand scale).
The lung is divided into nine horizontal slices and the position of each slice is shown by its anterior rib marking. Table shows relative lung volume (Vol), ventilation (VA), perfusion (Q), ventilation-perfusion ratio (VA/Q), gas tensions (P O₂, P CO₂, P N₂), and respiratory exchange ratio (R) of each slice.

**TABLE 1. Effects of observed distribution of ventilation and perfusion on regional gas tensions**

<table>
<thead>
<tr>
<th>Vol %</th>
<th>VA/Q 1/min</th>
<th>V A/O</th>
<th>P O₂ mmHg</th>
<th>P CO₂ mmHg</th>
<th>P N₂ mmHg</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.24 0.07</td>
<td>3.3</td>
<td>132</td>
<td>28</td>
<td>553</td>
<td>2.0</td>
</tr>
<tr>
<td>8</td>
<td>0.33 0.19</td>
<td>1.8</td>
<td>121</td>
<td>34</td>
<td>558</td>
<td>1.3</td>
</tr>
<tr>
<td>10</td>
<td>0.42 0.33</td>
<td>1.3</td>
<td>114</td>
<td>31</td>
<td>562</td>
<td>1.1</td>
</tr>
<tr>
<td>11</td>
<td>0.52 0.50</td>
<td>1.0</td>
<td>108</td>
<td>39</td>
<td>566</td>
<td>0.92</td>
</tr>
<tr>
<td>12</td>
<td>0.59 0.66</td>
<td>0.90</td>
<td>102</td>
<td>40</td>
<td>571</td>
<td>0.85</td>
</tr>
<tr>
<td>13</td>
<td>0.57 0.83</td>
<td>0.80</td>
<td>98</td>
<td>41</td>
<td>574</td>
<td>0.78</td>
</tr>
<tr>
<td>13</td>
<td>0.72 0.98</td>
<td>0.73</td>
<td>95</td>
<td>41</td>
<td>577</td>
<td>0.73</td>
</tr>
<tr>
<td>13</td>
<td>0.78 1.15</td>
<td>0.68</td>
<td>92</td>
<td>42</td>
<td>579</td>
<td>0.68</td>
</tr>
<tr>
<td>13</td>
<td>0.82 1.29</td>
<td>0.63</td>
<td>89</td>
<td>42</td>
<td>582</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**TABLE 2. Blood gas contents and gas exchanges in the nine lung slices**

<table>
<thead>
<tr>
<th>VA/Q</th>
<th>Blood Gas Contents</th>
<th>Gas Exchange, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O₂ cont. vol %</td>
<td>CO₂ cont. vol %</td>
</tr>
<tr>
<td>1st space</td>
<td>3.3</td>
<td>0.0</td>
</tr>
<tr>
<td>2nd rib</td>
<td>1.8</td>
<td>19.9</td>
</tr>
<tr>
<td>2nd space</td>
<td>1.3</td>
<td>19.8</td>
</tr>
<tr>
<td>3rd rib</td>
<td>1.0</td>
<td>19.7</td>
</tr>
<tr>
<td>3rd space</td>
<td>0.90</td>
<td>19.6</td>
</tr>
<tr>
<td>4th rib</td>
<td>0.86</td>
<td>19.5</td>
</tr>
<tr>
<td>4th space</td>
<td>0.73</td>
<td>19.4</td>
</tr>
<tr>
<td>5th rib</td>
<td>0.08</td>
<td>19.3</td>
</tr>
<tr>
<td>5th space</td>
<td>0.63</td>
<td>19.2</td>
</tr>
<tr>
<td>Total</td>
<td>291</td>
<td>232</td>
</tr>
</tbody>
</table>

* O₂ contents differ slightly from those in Table 1 of a previous paper (8) where an erroneous correction for dissolved O₂ was used.

The corresponding maximum differences in carbon dioxide and nitrogen tensions are 14 and 29 mm Hg.

**FIG. 3. O₂-CO₂ diagram showing VA/Q line (curving down to right hand lower corner), which gives all possible O₂ and CO₂ tensions in a lung inspiring air and having mixed venous O₂ and CO₂ tensions of 40 and 45 mm Hg, respectively. Position of each of the 9 slices on this line is shown. Areas within large circles indicate relative ventilations (white) and blood flows (black), and therefore ventilation-perfusion ratio of each slice. Mixed alveolar (A) and mixed arterial (a) points can be seen on the respective R = 0.8 lines for gas and blood.**

must occur as a result of the distributions of ventilation and blood flow shown in Fig. 2. If no limitations of diffusion are assumed, the same gas tensions will be present in the end-capillary blood of these areas of the lung. The gas tensions of each lung slice were found by drawing the O₂-CO₂ diagram shown in Fig. 3; they are given in Table 1. It can be seen that the alveolar oxygen tension varies from 132 mm Hg in the highest slice to 89 mm Hg in the lowest, that is, a difference of 43 mm Hg. The corresponding maximum differences in carbon dioxide and nitrogen tensions are 14 and 29 mm Hg.
related to the ventilation-perfusion ratio.

side the normal range for arterial blood (9). A surprisingly high blood pH of 7.5
nitrogen will pass from blood to gas, whereas the reverse
of nitrogen gas out of the blood at the apex of the lung
of gas passing in each direction being about
exchange being zero. The result is a continual circulation
process occurs in the lower regions, the net nitrogen
blood in the upper regions of the lung so that here
will be lower than the nitrogen tension of mixed venous
oxygen, carbon dioxide, and nitrogen which exchange
between alveolar gas and pulmonary blood in the various
content appreciable, thus affecting the relationship
content of end-capillary blood by their
alveolar gas contribution of each lung slice by their
mixed alveolar gas and arterial blood as a result of the
oxygen difference (and therefore the largest alveolar-end capillary
dissociation curve (Table 2). Thus the change in oxygen
tension of 43 mm Hg down the lung corresponds to a
change in oxygen content or saturation of only 4%. This
buffering effect of the dissociation curve is important
when the over-all oxygen uptake of the lung is consi-
dered.

The percentage variation in carbon dioxide content
down the lung is about half as large as that of carbon
dioxide tension because of the slope of the dissociation
curve. A surprisingly high blood pH of 7.51 is calculated
in the uppermost lung slice, this value being well out-
side the normal range for arterial blood (9).

Volumes of gas exchanged. Table 2 gives the volumes of
oxygen, carbon dioxide, and nitrogen which exchange
between alveolar gas and pulmonary blood in the various
lungs. The oxygen uptake that occurs at each level
is closely related to the regional blood flow, because of
the small differences in oxygen content of end-capillary
blood (Table 2). Only in the lower slices is the fall in O2
close to the relationship
between oxygen uptake and blood flow. On the other
hand, the volume of carbon dioxide lost by each slice is
closely related to the local ventilation.

The nitrogen exchange is noteworthy. Canfield and
Rahn (10) showed that whether an alveolus loses or
knows nitrogen depends on its ventilation-perfusion ratio.
In the present lung model, the alveolar nitrogen tension
will be lower than the nitrogen tension of mixed venous
blood in the upper regions of the lung so that here
nitrogen will pass from blood to gas, whereas the reverse
process occurs in the lower regions, the net nitrogen
exchange being zero. The result is a continual circulation
of nitrogen gas out of the blood at the apex of the lung
and into the blood at the base (Fig. 4), the total volume
of gas passing in each direction being about 0.2 ml/min.

This small volume may be contrasted with the 4,000 ml
of nitrogen which pass the lips each minute.

Diffusion. So far the lung model has been built on the
assumption of no diffusion limitations. However, from
measurements made using radioactive carbon monoxide
(11, 12) it is possible to estimate whether regional
differences in diffusion properties will impede oxygen
transfer. Piiper (13) has shown that inequalities of the
diffusion-perfusion ratio may introduce an alveolar-
arterial oxygen difference even if the over-all diffusion-
perfusion ratio is normal.

The interpretation of regional differences in the
clearance rate of radioactive carbon monoxide is com-
plicated by the fact that the clearance rate measures not
only the rate of loss of carbon monoxide from alveolar
gas (which depends on the local diffusing capacity) but
also the regional blood flow. However, the latter factor
can be extracted using the clearance rate of radioactive
carbon dioxide, and so the local diffusing capacity can
be derived. Unfortunately the repeatability of the com-
bined measurements is poor, but approximate values
have been obtained. In most subjects, the diffusing
capacity per unit lung volume increases down the lung,
the ratio of the upper to lower zone values being between
0.5 and 1 (12).

If the diffusing capacity per unit lung volume is
assumed to increase linearly down the lung with a two-
fold difference between highest and lowest slices, diffu-
sion-perfusion ratios can be calculated, assuming a
diffusing capacity of the whole lung of 20 ml/min mm
Hg Calculations show that the lowest diffusion-perfusion ratio
(and therefore the largest alveolar-end capillary oxygen differ-
cence) is found in the lowest slice, a value of
2.6 X 10^-3 mm Hg^-1 being obtained. However, the
oxygen difference corresponding to this diffusion
limitation is less than 0.01 mm Hg. It follows from this
that the over-all alveolar-arterial oxygen difference
attributable to diffusion will also be less than 0.01 mm
Hg and that the assumption of no diffusion limitations
in the lung model, which was made earlier, is a reason-
able one.

Alveolar-arterial differences. The oxygen, carbon dioxide,
and nitrogen tension differences that develop between
mixed alveolar gas and arterial blood as a result of the
imposed ventilation-perfusion ratio inequality can be
calculated, and the results are shown in Table 1 and
Fig. 5. The calculations were made by weighting the
alveolar gas contribution of each lung slice by their
ventilation and the blood contributions by their per-
fusion. The tensions of the mixed alveolar gas and arterial
blood are thus derived. Figure 5 shows how the alveolar
(A) and arterial (a) points have moved away from the
"ideal" point, that is, the point which gives the alveolar
or arterial gas tensions for a lung that has the same
over-all respiratory exchange ratio but no uneven
distribution. The alveolar and arterial points have each
moved along their appropriate R lines (R = 0.8) and
the alveolar-arterial differences can be read off the graph.
The distance which the alveolar point has moved reflects

\[ \text{Distance} = R \times \text{Respiratory Exchange Ratio} \]

\[ \text{Respiratory Exchange Ratio} = \frac{\text{Alveolar}}{\text{Arterial}} \]
the wasted ventilation and, similarly, the arterial point moved because of wasted blood flow. It can be seen that of the 4 mm Hg oxygen difference, 3 are found in the blood and 1 in the gas phase; for the nitrogen almost all the 3 mm Hg difference is in the blood, while all the 1 mm Hg carbon dioxide difference is attributable to the mixed alveolar gas and, therefore, represents dead-space ventilation.

The total alveolar-arterial oxygen difference in erect man is about 10 mm Hg so that if 4 mm Hg is subtracted for a venous admixture component of 2% of the cardiac output, some 6 mm Hg remains to be accounted for by distribution. A similar conclusion was reached by Farhi and Rahn (14), who analyzed published data. The analysis presented here gives a 4 mm Hg oxygen difference and, considering that not all the lung is accessible to measurement by the radioactive gas technique, it seems probable that most of the uneven distribution in normal upright man is accounted for by the differences in blood flow and ventilation up and down the lung.

Over-all gas exchange. The prime function of the lung is to exchange oxygen and carbon dioxide between blood and air, and it is therefore pertinent to ask how far the ventilation-perfusion ratio inequality of the lung model interferes with over-all gas exchange. This question can be answered by adding the oxygen uptakes and carbon dioxide outputs of each lung slice and comparing the sums with the oxygen and carbon dioxide exchange of a lung which has the same ventilation and blood flow but no uneven distribution. For oxygen, the uptake for the lung with no unevenness is 296 ml/min and this falls to 291 ml/min when the ventilation-perfusion ratio inequality is imposed, a decrease of only 2%. For carbon dioxide, the output in the absence of uneven distribution is 238 ml/min and drops to 232 ml/min in the lung model, a fall of 3%.

These values emphasize the great resilience or "buffering action" of the lung and blood to uneven distribution, and this property is particularly marked in the case of oxygen because of the shape of the oxygen dissociation curve. In spite of regional differences in the alveolar (and end capillary) oxygen tensions of over 40 mm Hg, the over-all oxygen uptake is reduced by only 2%. Thus the striking inequality of blood flow which occurs as a result of standing up has little effect on those functions of the lung of importance to the organism as a whole.

INACCURACIES IN LUNG MODEL

It should be emphasized that the lung model does not purport to be an accurate representation of the average regional differences in upright man, but rather the aim is to portray the general pattern of gas exchange which will occur if blood flow and ventilation have the distribution indicated by the radioactive gas measurements. These measurements have limitations which should be borne in mind. In particular, the clearance rate of radioactive carbon dioxide measures the rate of loss of labeled blood from the counting field, not the pulmonary capillary blood flow directly (12).

It is also possible that there is ventilation-perfusion inequality within each lung slice which was not detected by the radioactive carbon dioxide measurements. For example, if the blood flow and ventilation of individual alveoli had a broad random distribution in addition to the steady increase down the lung, this would not be revealed by the relatively crude radioactive measurements, but gas exchange in the lung would be affected, resulting in larger alveolar-arterial gas differences. Thus the radioactive measurements indicate the minimal inequality of ventilation-perfusion ratios that must be present. In this respect, the reasonably good agreement between the calculated alveolar-arterial oxygen difference and published data is encouraging.

POSSIBLE HOMEOSTATIC MECHANISMS

Himmelstein et al. (15) demonstrated that alveolar hypoxia can reduce the blood flow to one lung although the effect occurs only when the inspired oxygen tension is reduced to 5%, and even then it is not invariably found. Severinghaus, Swenson, and their colleagues (16) have shown that a fall in alveolar carbon dioxide tension (after pulmonary artery obstruction) can decrease local ventilation by about 25%. Both these mechanisms might partly restore homoeostasis of gas exchange in a lung in which blood flow was disturbed by its host standing upright. The lower oxygen tension that followed the increased blood flow to the basal regions would tend to decrease this flow, while the lower carbon dioxide tension at the apex of the lung would decrease ventilation, thus partially restoring the local ventilation-perfusion ratio toward the over-all ratio for the whole lung.

OTHER MEASUREMENTS OF REGIONAL VENTILATION AND BLOOD FLOW

Two groups of investigators, Mattson and Carlens (3) and Martin and Young (17), have compared the ventilations and oxygen uptakes of the right upper lobe with the rest of the right lung in erect man by means of
a triple-lumen catheter. The two sets of results agree well and allow the relative ventilation-perfusion ratios of the right upper lobe and the rest of the right lung to be computed. To do this, it is assumed that the ratios of dead space to tidal volume of these two portions of the lung are the same and that their oxygen uptakes reflect their relative blood flows. This will be true in Mattson and Carlens' measurements, which were made with the subjects breathing pure oxygen, and nearly so with Martin and Young's experiments, in which air-filled spirometers were used.

Mattson and Carlens' results show that the average ventilation-perfusion ratio of the right upper lobe was 2.8 times that of the rest of the right lower lung, and the corresponding figure for Martin and Young was 2.2. These figures will underestimate the difference in ventilation-perfusion ratio between the uppermost and lowermost parts of the lung because both the upper lobe and lower (plus middle) lobe values will be averages for large portions of the lung. In addition, the shape of the lower lobe is such that it encroaches considerably on the upper part of the thoracic cage. For these reasons, the above figures will appreciably underestimate the ventilation-perfusion ratio difference between apex and base, and they seem to be compatible with the fivefold difference between the uppermost and lowermost slices of the lung model.

The first results of measurements of regional ventilation and blood flow in normal subjects using xenon 133 have recently been published (6). It is not yet clear how the counting fields which Ball and his colleagues used correspond to those of the oxygen 15 series, but because of the greater scattering of the weaker xenon radiation, it is likely that the areas of lung from which counts were accepted were appreciably larger in the case of xenon, and this makes direct comparison of the two sets of results difficult. Ball et al. found that the ventilation (per unit lung volume) of the lower lung zone compared with the upper was about 1:1.5, while the corresponding blood flow ratio was approximately 1:3. Both these ratios show less inequality than that indicated by the oxygen 15 measurements for the uppermost and lowermost slices of the lung, but if the xenon figures are taken to refer to the lung at the levels of the second and fifth ribs anteriorly, the corresponding ratios for oxygen 15 are 1:1.5 and 1:4, so that agreement between the two different techniques is apparently good.

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REFERENCES