Determination of the Pulmonary Capillary Blood Flow in Man

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Several different methods based on respiratory maneuvers have been developed for the measurement of the rate of pulmonary capillary blood flow in man. These methods fall into two groups: (1) those involving the determination of the CO₂ or O₂ content of arterial and mixed venous blood from an analysis of alveolar gas—the first of these “indirect Fick methods” was developed by Loewy and von Schröter in 1903; and (2) those based on either the uptake of an inert gas by pulmonary capillary blood or its elimination therefrom; the principle of these methods was first proposed by Bornstein in 1910 and developed by Krogh and Lindhard in 1912.

The use of the respiratory maneuver techniques for the measurement of pulmonary capillary blood flow has some advantages over the indicator-dilution, and direct Fick, methods. These include: (1) simplicity and (2) validity in subjects with intracardiac left-to-right shunts. Unfortunately, although the theoretical bases for the estimation of the pulmonary blood flow by respiratory maneuvers seem to be sound, in practice their application has been handicapped by a variety of technical difficulties, particularly the need for completing the test prior to the recirculation of the test gas in the lungs and for determining separately a group of variables which should be measured simultaneously.

The present report describes a new method, based on Bornstein’s principle, for the determination of the pulmonary capillary blood flow. It was designed to circumvent the major shortcomings of previous methods based on the same principle.

Methods

In the present method, nitrous oxide was used as the test gas. The pulmonary capillary blood flow was determined by the equation of Krogh and Lindhard:

\[ \dot{Q} = \frac{\dot{V}_{N_2O}}{\lambda N_2O} \cdot \overline{F_{N_2O}} \]

in which \( \dot{Q} \) = Pulmonary capillary blood flow per minute; \( \dot{V}_{N_2O} \) = Volume of N₂O absorbed per minute (BTPS); \( \lambda N_2O \) = Ostwald’s coefficient of solubility of nitrous oxide in blood at 37 C.; \( \overline{F_{N_2O}} \) = Mean fraction of N₂O in alveolar gas during the test (BTPS).

Since the coefficient of solubility (\( \lambda \)) is constant (0.466 for N₂O), the variables involved in the calculation of the flow are two: (1) the volume of N₂O absorbed per minute (\( \dot{V}_{N_2O} \)), and (2) the mean alveolar fraction of N₂O during the test (\( \overline{F_{N_2O}} \)). The values of these variables were obtained by the following procedure and calculations.

Procedure

All tests were performed with the subject in a supine position. The nose was closed by a nose-clip. By arranging in series a mouthpiece, a pneumotachograph, and a two-way valve, the subject could breathe either ambient air or a special gas mixture contained in a spirometer (Collins, 13.5 L). An infrared N₂O analyzer (Spinco, Model LB-1) connected to the mouthpiece allowed a continuous analysis of the concentration of N₂O in inspired and expired gas. The N₂O analyzer had an accuracy of 1 per cent of the full scale,
Figure 1
Schematic representation of the system used for the determination of the pulmonary capillary blood flow by the nitrous oxide (N\textsubscript{2}O) method in man. (PNT) pneumotachograph.

Time response of 0.1 second to 90 per cent, and a dead space of 0.1 ml. The pneumotachogram and the N\textsubscript{2}O concentration were recorded simultaneously with the electrocardiogram by means of an oscillographic recording apparatus (Electronics for Medicine). The relation of the subject to the apparatus is illustrated in figure 1.

The actual test involved the performance of a vital capacity maneuver at the end of a maximal expiration: at the end of the expiration, the tap of the two-way valve was turned to connect the subject to the spirometer. The subject then took a maximal inspiration followed by a maximal expiration, at the close of which the tap was restored to its original position, so that he again breathed ambient air. By using ambient air as the inspired gas, this vital capacity maneuver was repeated several times, at one- to three-minute intervals, until the spiographic tracings were consistent both in form and in their return to the baseline (fig. 2).

The tracing was considered suitable for analysis when, in three successive maneuvers, the difference between the initial and the final baselines was reproducible within a range of ±20 ml. After the tracing characteristic for the subject had been established, the air contained in the spirometer was replaced by a mixture of 80 per cent N\textsubscript{2}O and 20 per cent O\textsubscript{2}, and the vital capacity sequence was repeated one or more times. In each case, an interval of 20 to 30 minutes was allowed between successive tests to allow the elimination of the N\textsubscript{2}O which had been absorbed in the previous test.

Using this procedure, 56 determinations of the pulmonary capillary blood flow were made in 18 subjects with normal lungs. The sex, age, body surface area, and diagnosis of these subjects are shown in tables 1 and 2. In 12 of these subjects, the measurements were made immediately after the determination of the pulmonary blood flow by the direct Fick method. For the application of the direct Fick method, samples of mixed venous blood were collected from the pulmonary artery by cardiac catheterization, and the volume of expired air was measured in a Tissot gasometer; the O\textsubscript{2} content of the blood samples was measured by the manometric method of Van Slyke and Neill and the O\textsubscript{2} fraction in the expired air was determined in a micro-Scholander gas analyzer. The pulmonary residual volume of the 18 subjects was determined by the open-circuit method of Darling, Courand, and Richards.

Calculations

Calculation of the Volume of N\textsubscript{2}O Absorbed per Minute (V\textsubscript{N\textsubscript{2}O})

When the subject performs the vital capacity maneuver with air as the test gas, the volume expired is essentially equal to the volume inspired and the spiographic tracing returns to the original baseline; when N\textsubscript{2}O is substituted for air in the spirometer, the volume expired is less than the volume inspired and the spiographic tracing does not return to the original baseline (fig. 2). This difference can be attributed to: (1) absorption of N\textsubscript{2}O by the blood perfusing the pulmonary capillaries, and (2) absorption of N\textsubscript{2}O by the lung tissues. In separate studies (see below), it was shown that the lung tissues do not absorb any significant amount of N\textsubscript{2}O during a single breath of this gas. Therefore, the difference between the volume of the N\textsubscript{2}O mixture inspired and the volume expired during the vital capacity maneuver can be interpreted as a measure of the amount of N\textsubscript{2}O absorbed by the blood perfusing the pulmonary capillaries during the test.

In the actual calculation of the volume of N\textsubscript{2}O absorbed (V\textsubscript{N\textsubscript{2}O}), two additional points were taken into account. The first was the frequent return of the spiographic record to a level slightly above the baseline (rather than to the baseline) during the control periods, i.e., when the vital capacity maneuver was performed with air as the test gas; when it occurred, this pattern was found to be consistent for any single subject during any given series of tests. It was attributed to the combined effects of respiratory exchange ratio of less than 1.0 and to the loss of a small amount (1.3 ml/sec.) of the gas mixture from the circuit as gas is continuously sucked through the N\textsubscript{2}O analyzer. Since both of these factors are operative during the inhalation of either air or N\textsubscript{2}O, they were taken into account by subtracting the difference between the initial and the final baselines on air from the difference observed when the N\textsubscript{2}O mixture is used as the test gas.
Table 1

Comparison of the Pulmonary Capillary Blood Flow by the Direct Fick and by the \( N_2O \) Methods

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>B.S.A. (M²)</th>
<th>Diagnosis</th>
<th>( \dot{Q} ) (Fick) *</th>
<th>( \dot{Q} ) (( N_2O ))</th>
<th>Deviation of ( N_2O ) from Fick (means) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V.A.</td>
<td>F</td>
<td>47</td>
<td>1.54</td>
<td>Normal</td>
<td>6.2</td>
<td>6.2</td>
<td>7.0</td>
</tr>
<tr>
<td>L.D.</td>
<td>M</td>
<td>57</td>
<td>1.92</td>
<td>Normal</td>
<td>7.0</td>
<td>7.0</td>
<td>8.3</td>
</tr>
<tr>
<td>R.N.</td>
<td>M</td>
<td>24</td>
<td>2.0</td>
<td>Normal</td>
<td>6.3</td>
<td>6.3</td>
<td>5.5</td>
</tr>
<tr>
<td>M.K.</td>
<td>M</td>
<td>34</td>
<td>1.93</td>
<td>Normal</td>
<td>5.5</td>
<td>6.25</td>
<td>7.3</td>
</tr>
<tr>
<td>A.A.</td>
<td>M</td>
<td>45</td>
<td>1.83</td>
<td>Normal</td>
<td>6.8</td>
<td>6.35</td>
<td>7.0</td>
</tr>
<tr>
<td>S.T.</td>
<td>M</td>
<td>63</td>
<td>1.78</td>
<td>Normal</td>
<td>5.1</td>
<td>5.1</td>
<td>4.9</td>
</tr>
<tr>
<td>L.S.</td>
<td>F</td>
<td>33</td>
<td>1.63</td>
<td>Normal</td>
<td>4.5</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>P.J.</td>
<td>M</td>
<td>50</td>
<td>2.04</td>
<td>Normal</td>
<td>4.5</td>
<td>4.6</td>
<td>5.1</td>
</tr>
<tr>
<td>A.B.</td>
<td>F</td>
<td>42</td>
<td>1.56</td>
<td>Mitral stenosis</td>
<td>5.0</td>
<td>5.0</td>
<td>4.4</td>
</tr>
<tr>
<td>A.A.</td>
<td>F</td>
<td>49</td>
<td>1.93</td>
<td>Mitral stenosis</td>
<td>3.2</td>
<td>3.2</td>
<td>2.9</td>
</tr>
<tr>
<td>V.C.</td>
<td>M</td>
<td>54</td>
<td>1.8</td>
<td>Heart failure</td>
<td>3.7</td>
<td>3.7</td>
<td>3.5</td>
</tr>
<tr>
<td>N.F.</td>
<td>M</td>
<td>27</td>
<td>1.71</td>
<td>Cooley's anemia</td>
<td>7.7</td>
<td>8.4</td>
<td>7.4</td>
</tr>
</tbody>
</table>

\*\( \dot{Q} \) = Pulmonary capillary blood flow per minute.

inspired gas. The second point was the elimination of nitrogen from the blood into the alveoli during the vital capacity maneuver, since the \( N_2O \) mixture used for the test is nitrogen-free (80 per cent \( N_2O \) and 20 per cent \( O_2 \)). The nitrogen elimination was corrected for by multiplying the volume of \( N_2O \) absorbed (as measured from the spirographic tracing) by a factor equal to

\[
1 - (0.03 \times \frac{0.80}{F_{N_2O}})
\]

where \( F_{N_2O} \) is the fraction of \( N_2O \) (STPD) in the inspired mixture (Appendix 1).

In practice, the volume of \( N_2O \) absorbed during the test was therefore obtained by: (1) measuring the difference between initial and final baselines (ml., BTPS) when the vital capacity maneuver was performed with \( N_2O \) as the test gas, (2) subtracting from that value the difference between initial and final baselines (ml., BTPS) observed when the vital capacity had been performed with air as the test gas, and (3) multiplying the difference between (1) and (2) by the correction factor for the nitrogen eliminated during the test with \( N_2O \) as the test gas.

The duration of the vital capacity maneuver was measured from either the spirographic tracing or the pneumotachographic record. To the measured time, 0.75 second was added to correct for the \( N_2O \) absorbed by the blood remaining in the pulmonary capillary bed at the close of the test. The correction factor corresponds to the mean time which blood is believed to spend in the pulmonary capillary bed.\(^13\)

From the volume of \( N_2O \) absorbed during the test and the duration of the test, the volume of \( N_2O \) absorbed per minute (\( \dot{V}_{N_2O} \)) was calculated.

Calculation of the Mean Alveolar Fraction of \( N_2O \) (\( \bar{F}_{N_2O} \))

The calculation of the mean alveolar fraction of
Table 2
Repeated Measurements of Pulmonary Capillary Blood Flow by the N₂O Method

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>B.S.A. (M²)</th>
<th>Diagnosis</th>
<th>Date</th>
<th>Q (L./min.)</th>
<th>Mean Q (L./min.)</th>
<th>Mean deviation (% of the mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.L.</td>
<td>M</td>
<td>32</td>
<td>2.07</td>
<td>Normal</td>
<td>8/27/59</td>
<td>8.3</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>V.A.</td>
<td>F</td>
<td>47</td>
<td>1.54</td>
<td>Normal</td>
<td>11/13/59</td>
<td>7.6</td>
<td>7.6</td>
<td>0.70</td>
</tr>
<tr>
<td>L.D.</td>
<td>M</td>
<td>57</td>
<td>1.92</td>
<td>Normal</td>
<td>11/20/59</td>
<td>8.3</td>
<td>8.85</td>
<td>0.55</td>
</tr>
<tr>
<td>M.K.</td>
<td>M</td>
<td>34</td>
<td>1.93</td>
<td>Normal</td>
<td>12/10/59</td>
<td>7.3</td>
<td>6.65</td>
<td>0.35</td>
</tr>
<tr>
<td>R.L.</td>
<td>M</td>
<td>31</td>
<td>1.91</td>
<td>Normal</td>
<td>12/20/59</td>
<td>7.5</td>
<td>7.25</td>
<td>0.25</td>
</tr>
<tr>
<td>L.G.D.</td>
<td>M</td>
<td>34</td>
<td>2.19</td>
<td>Normal</td>
<td>12/29/59</td>
<td>8.0</td>
<td>8.25</td>
<td>0.25</td>
</tr>
<tr>
<td>S.T.</td>
<td>M</td>
<td>63</td>
<td>1.78</td>
<td>Normal</td>
<td>1/5/60</td>
<td>4.9</td>
<td>5.1</td>
<td>0.20</td>
</tr>
<tr>
<td>L.S.</td>
<td>F</td>
<td>33</td>
<td>1.63</td>
<td>Normal</td>
<td>1/13/60</td>
<td>4.4</td>
<td>5.05</td>
<td>0.65</td>
</tr>
<tr>
<td>R.M.</td>
<td>M</td>
<td>22</td>
<td>1.8</td>
<td>Normal</td>
<td>2/11/60</td>
<td>6.2</td>
<td>6.0</td>
<td>0.27</td>
</tr>
<tr>
<td>R.N.</td>
<td>M</td>
<td>24</td>
<td>2.0</td>
<td>Normal</td>
<td>2/12/60</td>
<td>7.2</td>
<td>6.8</td>
<td>0.53</td>
</tr>
<tr>
<td>A.A.</td>
<td>M</td>
<td>45</td>
<td>1.83</td>
<td>Normal</td>
<td>5/11/60</td>
<td>7.0</td>
<td>6.0</td>
<td>0.62</td>
</tr>
<tr>
<td>V.C.</td>
<td>M</td>
<td>54</td>
<td>1.83</td>
<td>Heart failure</td>
<td>7/24/59</td>
<td>3.5</td>
<td>3.35</td>
<td>0.15</td>
</tr>
<tr>
<td>X.F.</td>
<td>M</td>
<td>27</td>
<td>1.71</td>
<td>Cooley's anemia</td>
<td>1/8/60</td>
<td>7.4</td>
<td>7.9</td>
<td>0.50</td>
</tr>
<tr>
<td>K.S.</td>
<td>F</td>
<td>14</td>
<td>1.43</td>
<td>Interventricular septal defect</td>
<td>2/12/60</td>
<td>8.7</td>
<td>9.0</td>
<td>0.20</td>
</tr>
<tr>
<td>T.S.</td>
<td>F</td>
<td>14</td>
<td>1.59</td>
<td>Interatrial septal defect</td>
<td>2/24/60</td>
<td>8.8</td>
<td>8.4</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Q = Pulmonary capillary blood flow per minute.
Typical spirographic tracings obtained from normal subjects during the performance of the vital capacity maneuver using a mixture of 80 per cent nitrous oxide in oxygen ($N_2O$) and ambient air (AIR) as the inspired gases. The tracings with $N_2O$ as the test gas were obtained at 30-minute intervals and those with ambient air at 2-minute intervals. The records were inscribed in the usual way from right to left, so that inspiration appears as the right limb (upstroke) of the tracings and expiration as the return of the tracings toward the baseline.

$N_2O$ for the entire vital capacity maneuver involved different approaches for expiration and for inspiration.

The mean alveolar fraction of $N_2O$ during expiration ($F_{A N_2O}$) was measured directly from the continuous record obtained by the $N_2O$ analyzer (fig. 3). Since the record at the very beginning of the expiration reflects gas in the dead space rather than in the alveoli, the alveolar fraction of $N_2O$ at the beginning of expiration was calculated by extrapolating backwards the sloping line which represents the changing fraction of alveolar $N_2O$, as shown in figure 3. This procedure is justified by the fact that the record of the alveolar fraction of $N_2O$ during expiration follows an essentially straight line. Knowing the alveolar fraction of $N_2O$ at the beginning ($A$) and at the end of expiration ($B$), and since these points are united by an essentially straight line (see fig. 3), the mean expired alveolar fraction of $N_2O$ was calculated as the arithmetic average of the initial and final values.

The mean alveolar fraction of $N_2O$ during inspiration ($F_{A N_2O}$) was calculated in two different ways. In the first, the $F_{AN_2O}$ was calculated from the residual volume (independently determined), the volume of the gas mixture inspired (measured from the spiographic record), and the fraction of $N_2O$ in this mixture (measured from the record obtained by the $N_2O$ analyzer). Figure 4 shows an example of this calculation. For this calculation it was assumed: (1) that inspiration is performed at a constant flow rate; this assumption is supported by the straightness of the ascending (inspiratory) limb of the spiographic curve as shown in figure 2, and (2) that the alveolar fraction of $N_2O$ during inspiration is not significantly modified by the volume of $N_2O$ absorbed by the blood perfusing the pulmonary capillaries during inspiration; that the error involved in this assumption is small is indicated by the fact that the alveolar fraction of $N_2O$ at the end of inspiration, calculated by this method, checks within ±0.02 with the alveolar fraction at the beginning of the expiration, measured from the $N_2O$ record.

The second approach was more expedient and precise. It involved the calculation of the mean alveolar fraction of $N_2O$ during inspiration ($F_{AN_2O}$) by the following equation which is based...
Figure 3
Record of the nitrous oxide concentration (\(N_2O\)), the pneumotachogram (PNT), and the electrocardiogram (ECG) obtained during the performance of the vital capacity maneuver using 80 per cent \(N_2O\) in oxygen as the inspired gas. (A) and (B) represent the alveolar concentration of \(N_2O\) at the beginning and at the end of the expiration, respectively. The interval between successive vertical time lines equals one second. The upward deflections of the pneumotachogram occur during inspiratory flow. The delay between corresponding deflections of the pneumotachogram and the \(N_2O\) tracing is a measure of the time required for the gas sample to reach the cell of the \(N_2O\) analyzer illustrated in figure 1.

on the same data and on the same assumptions as in the first approach (Appendix II):

\[
\bar{F}_{AN_2O_1} = F_{AN_2O} \frac{F_{1N_2O} \cdot RV}{V_{1N_2O}} \cdot \ln \frac{RV + V_{1N_2O}}{RV},
\]

where

\(\bar{F}_{AN_2O_1}\) = Mean alveolar fraction of \(N_2O\) during inspiration (BTPS);

\(F_{1N_2O}\) = Fraction of \(N_2O\) in the inspired mixture (BTPS);

\(RV\) = Residual volume of the subject;

\(V_{1N_2O}\) = Volume of the \(N_2O\) mixture inhaled by the subject (BTPS);

\(\ln\) = Natural logarithm.

In this equation, \(F_{AN_2O}\) is measured from the \(N_2O\) analyzer record, \(RV\) is determined independently, and \(V_{1N_2O}\) is measured from the spiographic tracing.

On occasion, the ascending (inspiratory) limb of the spirogram does not follow a straight line. Under these circumstances, it can be divided in two or more segments which can be considered, individually, as straight lines so that the mean alveolar fraction during inspiration (\(\bar{F}_{AN_2O_1}\)) can be calculated as indicated below (see Appendix II). In none of our cases was it necessary to divide the ascending limb of the spirogram into more than two segments.

Knowing the mean alveolar fraction of \(N_2O\) during inspiration and expiration, the mean alveolar concentration during the entire vital capacity maneuver was calculated as follows:

\[
\overline{F_{AN_2O}} = \frac{\bar{F}_{AN_2O_1} \cdot t_i + \bar{F}_{AN_2O_E} \cdot t_e}{T},
\]

where

\(\bar{F}_{AN_2O}\) = Mean alveolar fraction of \(N_2O\) during the vital capacity maneuver;

\(\bar{F}_{AN_2O_1}\) = Mean alveolar fraction of \(N_2O\) during inspiration;

\(\bar{F}_{AN_2O_E}\) = Mean alveolar fraction of \(N_2O\) during expiration;

\(t_i\) = Time duration of inspiration;

\(t_e\) = Time duration of expiration;

\(T\) = Time duration of the vital capacity maneuver (\(t_i + t_e\)).

Auxiliary Studies

For the validation of the \(N_2O\) method described above, two additional independent studies were undertaken: (1) the determination of the pulmonary recirculation time, and (2) the determination of the absorption of \(N_2O\) by the lung tissues.

Determination of the Pulmonary Recirculation Time

The formula used for the calculation of the blood flow (\(\dot{Q} = \dot{V}_{N_2O} / \lambda N_2O \cdot \overline{F_{AN_2O}}\)) is based on the assumption that the concentration of \(N_2O\) in the mixed venous blood equals zero. This is only true before \(N_2O\) recirculates in the pulmonary capillaries; after this, the actual concentration of \(N_2O\) in mixed venous blood cannot be disregarded. Since this concentration is not measured, it is essential for the application of this formula that the vital capacity maneuver be completed before appreciable pulmonary recirculation of \(N_2O\) had time to occur. The system illustrated in
PULMONARY CAPILLARY BLOOD FLOW

Figure 5 was used to determine the time at which pulmonary recirculation may be expected to occur. This system included a bronchospirometric tube and two separate open circuits so that the air breathed by each lung could be independently and continuously analyzed for its concentration of N₂O through two separate infrared analyzers (Spinco, model LB-1). The arrangement of the apparatus allowed the simultaneous recording, by means of the oscillographic recording apparatus, of the changing concentration of N₂O from both lungs, and the pneumotachogram from one of the lungs. The test procedure involved the following steps. After a maximal expiration, the subject took a deep inspiration which delivered ambient air into one lung and a mixture of 80 per cent N₂O in oxygen into the other. This maximal inspiration was followed by a very slow expiration which lasted for 20 to 30 seconds. The appearance of N₂O in the air exhaled by the lung which had received the ambient air was taken to indicate the time of pulmonary recirculation (fig. 6). A correction of 1 ± 0.3 second was made for the time taken by the air to move from the alveoli to the point of sampling next to the mouth. * Eleven determinations in four subjects (W.T., W.D., G.B., and V.H., in fig. 9) were done by this technique.

In the course of these determinations it was observed that, at the moment that N₂O appeared in the expirate of the lung which had breathed ambient air, the concentration of N₂O in the expirate from the opposite lung, i.e., the N₂O breathing lung, showed an upward change in slope (fig. 6). This change in slope appeared whenever the expiration was performed slowly and at a practically constant flow rate. The identification of this change in slope as evidence of first recirculation of inspired N₂O made it possible to determine the pulmonary recirculation time without recourse to bronchospirometry. Fifteen determinations in eight subjects were done by this latter technique.

*The value of this correction was calculated assuming that the expiratory flow rate was constant, as shown in figure 6. The correction was taken as the time necessary to exhale a volume of gas equivalent to that of the dead space of the subject plus that of the bronchospirometric tube up to the point of sampling (see fig. 5).

Example: 2,000 ml. of gas mixture were exhaled by the right lung of a subject in 20 seconds. The dead space (of the subject—bronchospirometry system) was calculated to be 100 ml. Since the flow was assumed to be constant, the time necessary to deliver the 100 ml. i.e., the volume of the dead space, was one second.

In three of these eight subjects, the determination of recirculation time from the change in the slope of the N₂O record was made during cardiac catheterization. As a further check on the change-slope method, blood samples were withdrawn from the pulmonary artery at five-second intervals, immediately following the inspiration of N₂O, so that the first appearance of N₂O in mixed venous blood could be determined. The concentration of N₂O in blood was determined in a Van Slyke manometric apparatus. 14

Determination of the Absorption of N₂O by the Lung Tissues

To distinguish between this factor and the volume of N₂O absorbed by the blood perfusing the pulmonary capillaries during the performance of the vital capacity maneuver, the following measurements were made on both dog and human lungs. The lungs were obtained shortly after death and made bloodless by gravitational emptying and washing with water. To measure the rate of absorption of N₂O by the lungs, the system illustrated in figure 7 was used. Air of lungs was placed in a plethysmograph. The trachea was connected by a hose to a spirometer (Collins 6L) placed outside the plethysmograph. A stopcock in the hose allowed the interruption of flow between the lungs and the spirometer. The alveolar air of the lungs was continuously sampled through a thin plastic tube placed deep within the bronchial tree. The air sampled was analyzed for N₂O by means of the infrared analyzer and recorded simultaneously with the plethysmographic pressure, using a transducer (Statham P23-2D-250) coupled to the oscilloscopic recording apparatus. The actual procedure involved the following steps: Air from the spirometer was pushed into the lungs until they appeared to be inflated to their normal size. The stopcock in the hose was then closed, avoiding the return of air to the spirometer. The pressure in the plethysmograph and the concentration of N₂O in the alveolar air were recorded prior to the inflation of the lungs and for the twenty seconds after inflation. The lungs were then deflated by opening the stopcock and withdrawing the air back into the spirometer. The test was then repeated, substituting N₂O for air as the test gas in the spirometer. Care was taken to introduce identical amounts of air and N₂O in successive runs. The procedure was carried out twice on dog lungs and six times on human lungs.

Results

The results obtained in this study fall into five categories: (1) values obtained for the pulmonary capillary blood flow by the N₂O method; (2) comparison of the values ob-
Values Obtained for the Pulmonary Capillary Blood Flow by the N₂O Method

The results obtained in 56 determinations of the pulmonary capillary blood flow by the N₂O method are shown in tables 1 and 2. In the 12 normal subjects studied in this series, the pulmonary capillary blood flow averaged 6.3 L./min. The cardiac index averaged 3.38 L./min./M² in the normal subjects, 2.06 L./min./M² in the patients with mitral stenosis and heart failure, and 5.45 L./min./M² in the group of patients expected to have abnormally large pulmonary blood flows from either Cooley's anemia or left-to-right intracardiac shunts.

Comparison of the Values Obtained by the Direct Fick and the N₂O Methods

Table 1 shows the individual and mean values for the pulmonary capillary blood flow obtained in 12 subjects by the direct Fick and the N₂O methods. The average of the mean values obtained by the N₂O method (5.65 L./min.) was 2 per cent higher than that ob-

*The blood flow measured by the N₂O method should differ from that measured by the direct Fick method by a fraction corresponding to the anatomic pulmonary arteriovenous shunt; the latter is not detected by the N₂O method. Nevertheless, since this fraction is very small in subjects with normal lungs (0.6 per cent of the total pulmonary blood flow), it can be assumed that both methods should yield virtually identical values.

Figure 4
Calculation of mean alveolar fraction of N₂O during the inspiratory phase (FₐN₂Oᵢ) of a vital capacity maneuver using a mixture of N₂O in oxygen (0.75 N₂O, BTPS) as the test gas. This illustration presupposes: (1) that the inspired volume equals the vital capacity of the subject; (2) that the vital capacity equals 60 per cent and the residual volume 20 per cent of the total lung capacity (TLC) of the subject; and (3) that the air flow rate is constant, i.e., t₁ = t₂ = t₃ = t₄. By dividing the inspired volume into four equal parts (each one equal to the residual volume), the fraction of alveolar N₂O at points I, II, III, IV, and V may be calculated as follows:

\[
\begin{align*}
I &= 0; \\
II &= \frac{(0.1) + (0.75)1}{2} = 0.375; \\
III &= \frac{(0.375)2 + (0.75)1}{3} = 0.50; \\
IV &= \frac{(0.50)3 + (0.75)1}{4} = 0.551; \\
V &= \frac{(0.551)4 + (0.75)1}{5} = 0.60.
\end{align*}
\]

From the alveolar fraction of N₂O at each one of these points, the mean alveolar fraction of N₂O during the entire inspiration (FₐN₂O₁) may be calculated as follows:

\[
FₐN₂O₁ = \frac{0 + 0.375 + 0.375 + 0.50 + 0.50 + 0.551 + 0.551 + 0.60}{2 + 2 + 2 + 2 + 2} = 0.432.
\]
PULMONARY CAPILLARY BLOOD FLOW

tained by the direct Fick method (5.55 L./min.). The average of the deviations observed between the two methods was 11 per cent. In figure 8, the individual values obtained by the N₂O method for each subject are plotted against the mean value obtained for the same subject by the direct Fick method. This shows that: (1) in 20 of the 22 comparisons, the deviations between the individual results of the N₂O method and the mean results of the direct Fick method fall within a range of ± 20 per cent; and (2) there is no systematic deviation between the values obtained by the N₂O and the direct Fick methods. It should be noted that in both table 1 and figure 8, mean values obtained by the direct Fick method were used for comparison because the Fick and N₂O methods could only be applied in succession, rather than simultaneously.

Reproducibility of the Values Obtained by the N₂O Method

Table 2 illustrates the reproducibility of the results obtained when the test is repeated two or more times in the same patient at one sitting. The mean percentile deviation between successive determinations in each patient, ranged from 0 to 13 per cent, with an average of 6 per cent. The reproducibility of the results obtained when the test is repeated in the same patient, under the same conditions, on different days, was studied in subject R.N. (tables 1 and 2). Thirteen measurements, on five different days, showed a mean percentile deviation of 11 per cent.

Determination of Pulmonary Recirculation Time

The results of 26 determinations of the pulmonary recirculation time in 12 subjects are shown in figure 9. The values obtained ranged from 8 to 14 seconds with a mean of 11 seconds. In the three subjects in whom pulmonary arterial blood was sampled following the inhalation of N₂O, the first appearance of N₂O in blood corresponded to the time at which pulmonary recirculation was indicated by the change in slope of the record of the alveolar concentration of N₂O.

Absorption of N₂O by the Lung Tissues

The measurements indicate that no significant quantities of N₂O were absorbed by the lung tissues during the performance of the vital capacity maneuver: (1) the expansion of the lungs with identical amounts of air and N₂O in successive runs, increased the pressure in the plethysmograph to the same level, indicating that no absorption had occurred during the period of inflation of the lungs with N₂O; and (2) after the inflation of the lungs with N₂O was completed, the pressure in the plethysmograph remained constant (fig. 10), indicating that no absorption of N₂O took place during the period of sustained inflation.

Discussion

The method developed in the present study for the measurement of the pulmonary capillary blood flow is a variant of the Krogh and Lindhard's application of Bornstein's principle.²

Krogh and Lindhard Method

The Krogh and Lindhard method involved a deep inhalation from a spirometer containing the test N₂O mixture followed by a partial expiration (alveolar sample I), a period of breathholding, and the completion of the expiration (alveolar sample II). The flow during the period of breathholding was calculated from the volume of N₂O absorbed and the mean alveolar fraction of N₂O; the latter
Figure 6

Records obtained at two different paper speeds using the system illustrated in figure 5.
In both records, the vertical time lines occur at one-second intervals. The upper record represents a single vital capacity maneuver with the expiratory phase performed at a very slow and uniform rate. The lower record represents a similar maneuver followed by continuous record of the changes during a subsequent period of normal breathing. The upward deflections of the pneumotachogram (PNT) occur during expiratory flow. For the sake of clarity, the lower record has been redrawn and the changing concentration of $N_2O$ during each breath of the right lung ($N_2O\text{ RL}$) is represented as a dashed line. (ECG) electrocardiogram; (RL) right lung; (LL) left lung.

The value was calculated from the analysis of the two alveolar samples (collected at the beginning and at the end of the breathholding period) and from the spirometric tracing. Based on the alveolar gas samples, a correction was also introduced for the difference between the oxygen uptake of the subject during the test and his ordinary oxygen uptake.

Comparison Between the Present $N_2O$ Method and the Krogh and Lindhard Method

The present method differs from that of Krogh and Lindhard in the following aspects: (1) the test is performed in 10 seconds or less, thus avoiding pulmonary recirculation of the test gas; the Krogh and Lindhard method allowed 25 seconds for the breathing maneuver; (2) no correction is introduced (see below) for a supposed difference between the $O_2$ uptake during the test and the ordinary $O_2$ consumption; this omission reduced the collection of the data necessary for the calculation of the flow to a single respiratory maneuver; (3) the blood flow is measured during both the inspiratory and the expiratory phases of a vital capacity maneuver in order to take into account the opposing hemodynamic changes of inspiration and expiration; the Krogh and Lindhard method measured the flow only during the expiratory phase; and (4) a continuous $N_2O$ analyzer is substituted for the cumbersome collection and analysis of individual "alveolar" samples in order to simplify the determination of the mean alveolar $N_2O$ concentration; this change simplified the procedure considerably without appreciable sacrifice of accuracy.

Potential Sources of Error in the Present $N_2O$ Method

Measurement of the Volume of $N_2O$ Absorbed ($\dot{V}_{N_2O}$)

Three sources of error are inherent in the present method for measuring $\dot{V}_{N_2O}$: (1) in-
accuracy in measuring volume and time from
the spirometric tracing (± 2 ml. and ± 0.1 second with a 13.5 L. Collins spirometer); these inaccuracies can be shown to introduce a potential error of the order of ± 2 per cent in the calculated pulmonary blood flow; (2) inaccuracy in estimating the time spent by the blood in the pulmonary capillaries; up to 30 per cent variation in the mean value assumed for this variable (0.75 second) may introduce an error of ± 2 per cent in the calculated flow; and (3) inability of the patient to perform the vital capacity maneuver in a consistent way; this difficulty is easily detected during the control period (using air as the test gas) and its influence can be reduced to a minimum as shown by the reproducibility of successive measurements (fig. 2 and table 2).

Calculation of the Mean Alveolar Fraction of N2O
\( \bar{F}_{alve} \)

Since the mean alveolar fraction of N2O during expiration is measured directly from the continuous N2O analyzer record, it presumably involves an error which is no greater than ± 0.01. On the other hand, the calculation of the mean alveolar fraction of N2O during inspiration involves certain assumptions. The magnitude of the errors introduced by these assumptions has been assessed by comparing the values obtained for the alveolar N2O concentration at the end of the inspiration (by the equations based on those assumptions) with the values measured from the N2O analyzer record (point A, fig. 3). Such comparisons have shown that the assumptions can introduce an error of the order of ± 0.02 in the calculation of the mean alveolar fraction of N2O during inspiration. Based on these considerations, the total error in the mean alveolar fraction of N2O may lead to an error of ± 3 per cent in the value of the pulmonary capillary blood flow.

In the calculation of the mean alveolar fraction of N2O, by the present method, a completely uniform distribution of N2O throughout the lungs during the performance of the vital capacity maneuver was not assumed. On theoretical grounds, such an assumption appears to be unnecessary: The unevenness of the distribution which is characteristic of subjects with normal lungs should not affect the validity of the calculation. According to Henry's law, the absorption of the test gas in each area of the lung is directly proportional to the concentration of the test gas in that area. Since only the mean alveolar concentration of N2O is considered in the calculation of the blood flow, no appreciable error will be intro-
The pulmonary recirculation time in 12 normal subjects. In each case, the position of the oval represents the average recirculation time. The range is indicated by the height of the vertical lines between the horizontal markers. The number within each oval indicates the number of separate determinations for the subject.

duced if: (1) all the areas of the lungs receive some N₂O during the single, deep inhalation of this gas; and (2) the ventilation/perfusion relationships are not appreciably disturbed. These conditions are apt to be fulfilled in the absence of pulmonary disease.

**Pulmonary Residual Volume of the Subject**

The residual volumes were measured either before or after the test on the assumption that they remained constant. Indeed, small differences in the residual volume will have no measurable effect on the calculated value for the blood flow. This is due to the fact that the value for the residual volume is only used in the calculation of the mean alveolar fraction of N₂O during inspiration which is the shortest part of the test. It can be shown that a difference of 10 per cent in the residual volume will introduce an error of only 1 to 2 per cent in the value of the pulmonary capillary blood flow. These considerations indicate that, for normal subjects, the use of the predicted value of the residual volume (based on the vital capacity and the age of the patient) instead of the actually measured value, will not introduce any serious error in the calculation of the pulmonary capillary blood flow.

**Correction for an Increase in the O₂ Uptake During the Test**

The correction factor used by Krogh and Lindhard for an increase in O₂ uptake during the breathing maneuver was not used in the present method. This point warrants further consideration. Krogh and Lindhard observed an increased O₂ uptake during the test as compared to that observed in normal resting state. They attributed this difference to an increase in the pulmonary blood flow produced by the respiratory maneuver. On the basis of this conclusion, they multiplied the value of the flow measured during the test by a factor equal to the ratio of the O₂ uptake in normal resting state divided by the O₂ uptake during the test. Since the increase in O₂ uptake which they observed was quite impressive (averaging 38.5 per cent of the normal resting state value), their correction led to a marked reduction in their values for the pulmonary blood flow. Thus, in their original series, 34 determinations of the pulmonary blood flow in four normal subjects, in a sitting position, gave a mean value of 5.63 L./min.; after the correction this value was reduced to 4.04 L./min. With the subsequent modifications of the original formula by Lindhard and their adoption by Marshall and Grollman, this correction factor became inapparent albeit no less operative. As a result, later investigators failed to take this correction factor into proper account when searching for the bases for the discrepancies between the low values yielded by the Krogh and Lindhard method (or the derivative acetylene method) and the higher values provided by the direct Fick and the indicator-dilution methods.

The validity of the correction introduced by Krogh and Lindhard is suspect on two accounts: (1) alternative explanations are available, and (2) an increase in O₂ uptake during the test is not an invariable phenomenon. Haldane and Henderson attributed the observed increase in O₂ uptake to incomplete mixing of the gases. In the experiments of Marshall and Grollman, increased O₂ uptake was observed during the test in most of their cases, but in some instances the O₂
uptake during the test was actually less than during the resting pretest state. On the other hand, Armitage and Arnott\textsuperscript{22} found a significant increase in \( O_2 \) uptake when normal subjects, in a sitting position, performed successive vital capacity maneuvers; the increment was less (by two-thirds) when the subjects were tested in the supine position and failed to occur if more than two vital capacity maneuvers were performed. The authors attributed the increased \( O_2 \) uptake to an increased entry of blood in the lungs during the maneuver; in the supine position, the capacity of the lungs to accommodate additional blood would be smaller than in the upright position, and a limit would be reached promptly.

In the present method, the correction factor used by Krogh and Lindhard was omitted on the following grounds: (1) assuming with Armitage and Arnott\textsuperscript{22} that a vital capacity maneuver really does increase the \( O_2 \) uptake and the entry of blood in the lungs, this increase would seem to be insignificant when the maneuver is performed in the supine position and the subject has already performed the maneuver two or more times; and (2) no systematic difference was observed in the 22 comparisons made in this study between the direct Fick and the present \( N_2O \) method; if the breathing maneuver increased the pulmonary blood flow appreciably, systematic higher values should have been obtained with the \( N_2O \) method.

**Early Recirculation of the Test Gas in the Lungs**

The recirculation of \( N_2O \) in the lungs, before the completion of the vital capacity maneuver, would make the values obtained for the pulmonary capillary blood flow artificially low. The measurements of the pulmonary recirculation time made in the present study show that, on the average, blood carrying \( N_2O \) first returns to the pulmonary capillaries 11, plus or minus 3, seconds after its inhalation. This indicates that no significant pulmonary recirculation of \( N_2O \) occurs during the test, since the vital capacity maneuver is performed in 5 to 10 seconds.

The pulmonary recirculation time was determined in this study for adult normal subjects. Both in children and in adults with intracardiac left-to-right shunts, the recirculation time is apt to be shorter. However, this contingency may be taken into account by: (1) the determination of the actual pulmonary recirculation time for the individual from an analysis of the changing slope of the alveolar \( N_2O \) concentration during expiration (see above), and (2) the performance of the vital capacity maneuver within the time limit set by the subject's recirculation time. It should also be noted, as shown in figure 6, that the amount of \( N_2O \) returning to the lungs during the first few seconds of recirculation is exceedingly small. Consequently, as long as the time used for the respiratory maneuver does not exceed the recirculation time by more
The changing concentrations of nitrous oxide ($N_2O$) and of nitrogen ($N_2$) during the expiratory phase of a vital capacity maneuver following a breath of 80 per cent $N_2O$ in oxygen. The $N_2O$ tracing is the mirror image of the $N_2$ tracing. At any point of the curve, the gradient between the $N_2$ in the mixed venous blood (80 per cent $N_2$) and in the alveoli is essentially of the same magnitude as the gradient between the $N_2O$ in the alveoli and in the mixed venous blood (0 per cent $N_2O$). This identity allows the calculation of the volume of $N_2$ eliminated from the blood during the vital capacity maneuver without knowledge of the pulmonary capillary blood flow. The delay between corresponding deflections of the $N_2$ and $N_2O$ tracings is due to a difference in the time responses of the different analyzers.

than a few seconds, no appreciable error is likely to be introduced into the calculated value for blood flow.

The technique used for the determination of the pulmonary recirculation time offers three advantages over the others heretofore used in man: (1) the appearance of the indicator substance ($N_2O$ in the present technique) was monitored continuously and not through successive samples collected at relatively large intervals (five seconds in most of the cases),6,23 (2) the monitoring for the appearance of the indicator substance could be begun as soon as the test gas had been inhaled, i.e., as early as four seconds after the start of inspiration; and (3) the circulatory path involved in the test for the recirculation time was identical with the path which blood carrying the test gas would be expected to pursue during the determination of the pulmonary capillary blood flow. The values obtained (8 to 14 seconds) agree well with those obtained by others using different techniques: Gladstone (10 seconds),6 and Chapman et al. (12 seconds).7 In particular, the results obtained by detecting recirculation as an upward deviation in the expiratory limb of the $N_2O$ continuous record confirm the observations of Gladstone23 and of Cander and Forster,24 who plotted the fraction of the test gas in alveolar samples against the times at which the alveolar samples were collected.

Absorption of $N_2O$ by the Lung Tissues

In the present method, the difference between the volume of $N_2O$ inspired and expired during a vital capacity maneuver, was attributed to absorption of the test gas by the blood perfusing the pulmonary capillaries ($V_{N_2O,p}$). If, under the circumstances of the test, the lung tissues were able to absorb a significant amount of $N_2O$, the calculated value for $V_{N_2O,p}$ would be artificially high, since it would include the volume of $N_2O$ absorbed by the lung tissues.

The lack of appreciable absorption of $N_2O$ by the lung tissues during the time of the
test found in the present measurements is in accord with earlier observations of Lee and DuBois who measured the uptake of \( \text{N}_2\text{O} \) by the lung tissues after one second of exposure of the dog lung to the test gas. On the other hand, Cander and Forster concluded, on the basis of an analysis of the changing concentration of expired alveolar gas with time, that appreciable quantities of the test gas (\( \text{N}_2\text{O} \) or acetylene) were absorbed by lung tissues during the test period. However, their conclusions are uncertain because of the inability to separate clearly in such experiments the uptake of the gas by the lung tissues from the uptake by the perfusing blood. It should be emphasized that the results of the present study do not pertain to the demonstration that homogenized lung tissues absorb appreciable quantities of nitrous oxide. They are concerned instead with the fact that during a single breath of a \( \text{N}_2\text{O} \) mixture, the quantity of \( \text{N}_2\text{O} \) absorbed is insignificant with respect to the calculation of the pulmonary capillary blood flow.

**Results Obtained with the Application of the Present \( \text{N}_2\text{O} \) Method**

The results obtained with the application of the present \( \text{N}_2\text{O} \) method show that: (1) they correlate well (table 1) with the values obtained by the direct Fick method, and (2) they are reproducible. The correlation between the present \( \text{N}_2\text{O} \) method and the direct Fick method is of the same order of magnitude of that observed between Fick and dye-dilution methods by Hamilton and co-workers. Moreover, the reproducibility is similar to that observed with the direct Fick or the dye-dilution methods. Indeed, the analysis of the results shown in table 2 indicates that a mean deviation of more than 15 per cent between successive measurements by the \( \text{N}_2\text{O} \) method points to a technical error in the determinations.

**Limitations of the Present \( \text{N}_2\text{O} \) Method**

The present method has certain inherent limitations: (1) the cooperation of the patient is required for its accurate performance; (2) its use in patients with widespread lung disease is unreliable, since marked alterations in the distribution of the ventilation and/or in the ventilation/perfusion ratio can be expected to introduce significant errors in the calculation of the volume of \( \text{N}_2\text{O} \) absorbed and in the mean alveolar \( \text{N}_2\text{O} \) concentration; (3) its accuracy during exercise is uncertain because of the difficulty in performing a vital capacity maneuver.

**Summary**

A method is described for the measurement of the pulmonary capillary blood flow in human subjects with normal lungs. The method depends on the performance of a vital capacity maneuver using nitrous oxide as the test gas. It attempts to circumvent the deficiencies of previous respiratory methods by using an infrared analyzer for the continuous measurement of the concentration of \( \text{N}_2\text{O} \) in expired air, by ensuring that the respiratory maneuver is completed before recirculation occurs, and by determining simultaneously the values involved in the formula used for the calculation of the flow. As a basis for the method, the pulmonary recirculation time and the rate of \( \text{N}_2\text{O} \) absorption by the lungs were measured separately. The values for the pulmonary capillary blood flow obtained by the \( \text{N}_2\text{O} \) method correlate well with those obtained by the direct Fick method: In 12 subjects, the average value by the \( \text{N}_2\text{O} \) method was 5.65 L/min. in comparison with 5.55 L/min. by the direct Fick method; the mean percentile deviation between the values obtained by the two methods in each subject was 11 per cent. The results obtained by the \( \text{N}_2\text{O} \) method were also shown to be reproducible: In 14 subjects, successive measurements on the same occasion showed a mean percentile deviation of 6 per cent.

**Appendices**

Appendix I: Correction Factor for the Nitrogen Eliminated from the Blood into the Alveoli During the Vital Capacity Maneuver when Nitrous Oxide Is Used as the Test Gas

The correction factor was derived as follows:

When the vital capacity maneuver is performed with the \( \text{N}_2\text{O} \) mixture as the test gas, the volume of \( \text{N}_2\text{O} \) passing from the alveoli to the blood per-
fusing the pulmonary capillaries can be calculated by the formula

\[ V_{N_2O} = \dot{Q} \cdot \lambda N_2O \cdot (\overline{F}_{N_2O} - C_{N_2O}/100) \cdot t, \]  

where

\[ V_{N_2O} = \text{Volume of } N_2O \text{ dissolved in the blood during the vital capacity maneuver (BTPS)}; \]
\[ \dot{Q} = \text{Pulmonary capillary blood flow per second}; \]
\[ \lambda N_2O = \text{Ostwald's coefficient of solubility of } N_2O \text{ in blood at 37°C} (0.0466); \]
\[ \overline{F}_{N_2O} = \text{Mean alveolar fraction of } N_2O \text{ during the vital capacity maneuver (BTPS)}; \]
\[ C_{N_2O} = \text{Concentration of } N_2O \text{ in the mixed venous blood}; \]
\[ t = \text{Time duration of the vital capacity maneuver, in seconds}. \]

Before pulmonary recirculation of the \( N_2O \) dissolved in blood occurs, \( C_{N_2O} \) equals zero and equation 1 may be written

\[ V_{N_2O} = \dot{Q} \cdot \lambda N_2O \cdot \overline{F}_{N_2O} \cdot t. \]  

During the inhalation of the \( N_2O \) mixture, at the same time that the \( N_2O \) concentration rises in the alveolar air, the alveolar nitrogen is diluted by the nitrogen-free inspired mixture. A difference then exists between the concentration of nitrogen in the mixed venous blood and that in the alveoli. As a consequence, some nitrogen will be eliminated from the blood into the alveolar gas. The volume of nitrogen eliminated can be calculated by the formula

\[ V_{N_2} = \dot{Q} \cdot \lambda N_2 \cdot (C_{N_2}/100 - \overline{F}_{N_2O}) \cdot t, \]  

where

\[ V_{N_2} = \text{Volume of nitrogen eliminated from the blood into the alveoli during the vital capacity maneuver (BTPS)}; \]
\[ \dot{Q} = \text{Pulmonary capillary blood flow per second}; \]
\[ \lambda N_2 = \text{Ostwald's coefficient of solubility of nitrogen in blood at 37°C} (0.0147); \]
\[ C_{N_2} = \text{Concentration of nitrogen in the mixed venous blood (assumed to be 80 per cent at STPD and to remain constant provided the vital capacity maneuver ends before pulmonary recirculation occurs)}; \]
\[ \overline{F}_{N_2O} = \text{Mean alveolar fraction of } N_2O \text{ during the vital capacity maneuver (BTPS)}. \]

Calculating \( \overline{F}_{N_2O} \) (see Calculation of the Mean Alveolar Fraction of \( N_2O \)) and \( \overline{F}_{N_2} \) (by an approach similar to that used for the calculation of \( F_{N_2O} \)) and by means of a continuous nitrogen analyzer, it can be shown (see fig. 11) that when the nitrogen-free inspired mixture contains 80 per cent \( N_2O \) (STPD), \( \overline{F}_{N_2O} \) is essentially equal to \( C_{N_2}/100 - \overline{F}_{N_2O} \).

\[ \overline{F}_{N_2O} = C_{N_2}/100 - \overline{F}_{N_2O}. \]  

Dividing equation 2 by equation 3, substituting the equivalent value of \( \overline{F}_{N_2O} \) shown in equation 4, and solving for \( V_{N_2O} \),

\[ V_{N_2O} = V_{N_2O} \times \left( \frac{\lambda N_2}{\lambda N_2O} \right) = V_{N_2O} \times 0.03. \]  

When the fraction of \( N_2O \) in the inspired mixture (\( F_{N_2O} \)) differs from 0.80, \( V_{N_2} \) is corrected proportionately:

\[ V_{N_2} = V_{N_2O} \times 0.03 \times \frac{0.80}{F_{N_2O}}. \]  

Since \( V_{N_2O} \) equals the volume of \( N_2O \) absorbed, as measured from the spiographic tracing, plus the volume of nitrogen eliminated from the blood, it can be shown that its value equals the volume measured from the spiographic tracing times \( \frac{1}{1 - (0.03 \times \frac{0.80}{F_{N_2O}})} \).

Appendix II: Derivation of the Equation for the Calculation of the Mean Alveolar Fraction of Nitrous Oxide During the Inspiratory Phase of the Vital Capacity Maneuver (\( F_{N_2O} \))

In the derivation of this equation, it was assumed that during each segment (\( t_i \) to \( t_{i+1} \) on the spiogram): (1) inspiration is performed at a constant rate of air flow, and (2) the mean alveolar fraction of \( N_2O \) during inspiration is not appreciably altered by the volume of \( N_2O \) absorbed by the blood perfusing the pulmonary capillaries during inspiration. The validity of these assumptions was discussed in the text. The actual equation was derived as follows:

1. Symbols:
\[ r = \text{Residual volume of the subject (RV)}; \]
\[ v = \text{Inspired volume of } N_2O \text{ mixture (} V_{N_2O} \text{)}; \]
\[ t = \text{Time}; \]
\[ c = \text{Fraction of } N_2O \text{ in inspired gas (} F_{N_2O} \text{)}. \]


\[ x = \text{Fraction of } N_2O \text{ in the lungs at given time; } \]
\[ \overline{x} = \text{Mean fraction of } N_2O \text{ in the lungs during inspiration (} F_{N_2O} \text{)} ; \]
\[ T = \text{Total duration of inspiration.} \]

2. \[ \overline{x} = \frac{\int_0^T x \, dt}{T} . \] (1)

In general, \( v \) is a function of \( t \):

\[ v = f(t) . \] (3)

Substituting (3) in (1), and (1) in (2),

\[ \overline{x} = e - \frac{cr}{T} \int_0^T u(t) \, dt . \] (4)

Set

\[ u(t) = r + f(t) . \] (5)

From (4)

\[ \overline{x} = e - \frac{cr}{T} \int_0^T \frac{dt}{r + v} . \] (6)

Since \( v = r + v \)

\[ x = e - \frac{cr}{T} \int_0^T \frac{dt}{r + v} . \] (7)

3. Let us assume that the inspiration (ascending limb of the spiographic tracing) corresponds to one or more straight lines \( (1, 2, \ldots, n \text{ lines}). \)

Let us call \( v_1, v_2, \ldots, v_n \), the volume inspired and \( t_1, t_2, \ldots, t_n \), the time \( t \) at the end of each one of these lines. At the beginning of the first line \( v=0 \) and \( t=0 \). In the \( i \text{th line}, \) which applies between times \( t_{i-1} \) and \( t_i \), the volume inspired \((v_i)\) is

\[ v_i = v_{i-1} + a_i (t_i - t_{i-1}) , \] (8)

where \( a_i \) is the slope of the \( i \text{th line}. \)

Between \( t = t_{i-1} \) and \( t = t_i, v \) is

\[ v = v_{i-1} + a_i (t - t_{i-1}) . \] (9)

Substituting (9) in (7),

\[ \overline{x} = e - \frac{cr}{T} \sum_{i=1}^{n} \left[ \int_{t_{i-1}}^{t_i} \frac{dt}{r + v_{i-1} + a_i (t - t_{i-1})} \right] . \]

and integrating

\[ \overline{x} = e - \frac{cr}{T} \sum_{i=1}^{n} \frac{1}{a_i} \left[ \ln \frac{r + v_{i-1} + a_i (t - t_{i-1})}{r + v_i} \right] . \] (10)

(4) In the case in which the inspiration (ascending limb of the spiographic tracing) corresponds to one straight line \((n = 1), \) equation 10 becomes

\[ \overline{x} = e - \frac{cr}{T} \left[ \frac{1}{a} \ln \frac{r + v}{r} \right] . \] (11)

Since

\[ T_a = v . \]

Substituting symbols

\[ F_{N_2O} = F_{N_2O} - \frac{F_{N_2O} \cdot RV}{V_{N_2O}} \cdot \ln \frac{RV + v_{N_2O}}{RV} . \] (12)

In the case in which the inspiration (ascending limb of the spirogram) corresponds to two straight lines \((n = 2), \) equation 10 becomes

\[ \overline{x} = e - \frac{cr}{T} \left[ \ln \frac{r + v_1}{r} + \frac{1}{a_2} \ln \frac{r + v_2}{r + v_1} \right] . \] (13)

Since

\[ a_1 = \frac{v_1}{t_1} \quad \text{and} \quad a_2 = \frac{v_2 - v_1}{t_2} . \]

Substituting symbols

\[ F_{N_2O} = F_{N_2O} \cdot RV \left[ \frac{t_1}{v_1} \ln \frac{RV + v_1}{RV} ight] \]

\[ + \frac{t_2}{v_2 - v_1} \ln \frac{RV + v_2}{RV + v_1} . \] (14)

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