THE MEASUREMENT OF GASEOUS EXCHANGE DURING NITROUS OXIDE ANAESTHESIA

BY

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SUMMARY

A method is described for the estimation of carbon dioxide output, oxygen uptake, and respiratory exchange ratio during nitrous oxide anaesthesia. The inspired and expired minute volumes are measured with a box-bag system, the carbon dioxide concentrations with a carbon dioxide sensitive electrode, and the oxygen concentrations with a polarograph. Carbon dioxide output can be measured with a coefficient of variation of 1.1 per cent. The error in the measured oxygen uptake is largely dependent upon the total inspired oxygen but the error has a standard deviation of the order of 13 ml. Applications of the technique are discussed.

Body levels of carbon dioxide depend upon the balance between production and elimination, while oxygen levels result from the balance between intake and consumption. During anaesthesia, it is difficult to assess the rate of carbon dioxide production or oxygen consumption. This is unfortunate since carbon dioxide production and oxygen consumption are fundamental considerations in gaseous homeostasis, being, in fact, the reason for breathing.

DEFINITIONS

The oxygen consumption is the rate at which oxygen undergoes irreversible chemical change within the body. It may differ from the oxygen uptake measured at the mouth \( V_{O_2} \) by the amount deposited in or withdrawn from the body oxygen stores, which include the alveolar gas.

\[
\text{Oxygen uptake} = \text{oxygen consumption} \pm \text{oxygen transferred to or from body stores.}
\]

Since the body oxygen stores are small, there is seldom a large difference between uptake and consumption; therefore, uptake is usually an adequate measure of consumption.

As the inspired carbon dioxide is generally negligible, the output may be simply measured as the product of expired minute volume and the carbon dioxide concentration of the mixed expired gas:

\[
V_{CO_2} = V_E \cdot F_{ECO_2} \quad \text{(ii)}
\]

Values for gaseous exchange are expressed under conditions of standard temperature and pressure, dry (STPD).

The metabolic respiratory exchange ratio is the carbon dioxide production divided by the oxygen consumption and cannot be measured directly.
The expired gas respiratory exchange ratio \((R)\), formerly known as the respiratory quotient, is the carbon dioxide output divided by the oxygen uptake. It may be derived from inspired and expired gas:

\[
R = \frac{\text{\(V\)}\text{\(CO\)2}}{\text{\(V\)}\text{\(O\)2}} = \frac{\text{\(V\)}\text{\(E\)} \cdot \text{\(F\)}\text{\(E\)}\text{\(CO\)2} - \text{\(V\)}\text{\(E\)} \cdot \text{\(F\)}\text{\(E\)}\text{\(O\)2}}{\text{\(V\)}\text{\(I\)} \cdot \text{\(F\)}\text{\(I\)}\text{\(O\)2} - \text{\(V\)}\text{\(E\)} \cdot \text{\(F\)}\text{\(E\)}\text{\(O\)2}} \quad \text{(iii)}
\]

or from arterial and mixed venous blood:

\[
R = \frac{\text{\(V\)}\text{\(CO\)2}}{\text{\(V\)}\text{\(O\)2}} = \frac{\text{\(C\)}\text{\(V\)}\text{\(CO\)2} - \text{\(C\)}\text{\(a\)}\text{\(CO\)2}}{\text{\(C\)}\text{\(a\)}\text{\(O\)2} - \text{\(C\)}\text{\(V\)}\text{\(O\)2}} \quad \text{(iv)}
\]

The expired gas respiratory exchange ratio will equal the metabolic respiratory exchange ratio only when both oxygen and carbon dioxide are in a steady state, defined as a time when the body stores of each gas are constant.

In this paper we shall consider the problems of the measurement of gaseous exchange during nitrous oxide anaesthesia. In particular we have been concerned with the measurement of the respiratory exchange ratio for determination of the ideal alveolar oxygen tension by solution of the alveolar air equation (Rossier and Mean, 1943). Simultaneous determination of alveolar and arterial \(P\)\text{\(O\)2} is a valuable method of determination of shunts, maldistribution and diffusing capacity—all important factors governing the oxygenation of the arterial blood.

DIFFICULTIES WITH CONVENTIONAL METHODS OF MEASUREMENT OF GASEOUS EXCHANGE DURING ANAESTHESIA

Oxygen uptake.

There are two methods in common use—closed circuit spirometry and the Douglas bag technique. In the first, a spirometer is filled with a high concentration of oxygen and linked to the patient by a circle system with a soda lime canister. The oxygen consumption is indicated either by the descent of the bell or by the amount of oxygen which must be added to keep the spirometer trace level (Roth, 1922). The accuracy of this technique is not high \((\pm 7\) per cent). Since the descent of the spirometer bell indicates the net gas exchange less the carbon dioxide output, the measured "oxygen consumption" will include any exchange of inert gases. It is, therefore, essential that the tension of any inert gas remains constant during the period of measurement. This presents problems during nitrous oxide anaesthesia since equilibrium between the different compartments of the body is not attained for many hours (Severinghaus, 1954). Therefore, during a period of closed circuit breathing, nitrous oxide will pass from the blood into those body stores which are still unsaturated. The resultant fall in blood nitrous oxide will lower the alveolar nitrous oxide and so lead to a net loss of nitrous oxide from the spirometer.\(^*\) A further disadvantage of the closed circuit spirometer is that considerable modification of the system is required for the measurement of carbon dioxide output, since this gas is normally absorbed in the soda lime. For these reasons we have avoided the closed circuit spirometric method of measurement of oxygen uptake during anaesthesia.

The oxygen consumption may be determined more accurately \((\pm 2\) per cent) by the Douglas bag method which is based on equation (i) (Douglas, 1911). When the patient is breathing air, expired gas is collected for a measured period of time and analyzed for oxygen and carbon dioxide: the residuum is considered as nitrogen. The expired minute volume is determined directly by passing the contents of the Douglas bag through a gas meter: the inspired minute volume is determined as:

\[
\text{expired minute volume} \times \text{expired nitrogen concentration} = \text{inspired nitrogen concentration}
\]

It is assumed that the body nitrogen stores are in a steady state and that the number of molecules of nitrogen exhaled equal the number inhaled. This technique offers considerable difficulties during nitrous oxide anaesthesia. Firstly, it can never be assumed that the number of molecules of nitrous oxide inhaled is the same as the number exhaled. It is, therefore, impossible to compute the inspired minute volume by this method. Secondly, the determination of oxygen concentration in the presence of nitrous oxide is not simple. One of the authors (Nunn, 1958) has failed to adapt either the Haldane or the Scholander apparatus to this purpose. It is, in fact, necessary to resort to the mass spectrometer, polarograph, paramagnetic

\(^*\)If, during a closed circuit spirometer run, the nitrous oxide tension of the mixed venous blood (= tension in the spirometer) were to fall only 1 mm Hg (i.e. one part in about 300) the net loss of gas in the spirometer + functional residual capacity of the patient would amount to about 13 ml, which would appear as an error in the oxygen consumption.
A third method of measurement of oxygen consumption is the box-bag spirometer described by Donald and Christie (1949). We have been able to adapt this method to the conditions of nitrous oxide anaesthesia and it will be described in detail below.

**Carbon dioxide output.**

Compared with oxygen uptake, it is relatively simple to measure the carbon dioxide output of an anaesthetized patient when the inspired carbon dioxide is zero. It is only necessary to collect the expired gas and measure its volume and the fractional concentration of carbon dioxide. Measurement of volume presents no great difficulty and carbon dioxide concentration may be measured in the presence of nitrous oxide by infra-red analysis, modified Haldane apparatus (Nunn, 1958), or by the use of the carbon dioxide sensitive electrode (Severinghaus and Bradley, 1958).

**THE BOX-BAG TECHNIQUE FOR MEASUREMENT OF GASEOUS EXCHANGE DURING ANAESTHESIA**

Under any condition, the oxygen uptake and carbon dioxide output may be derived from the following measurements:

- Inspired minute volume.
- Expired minute volume.
- Inspired oxygen concentration.
- Expired oxygen concentration.
- Expired carbon dioxide concentration.

(It is assumed that the inspired carbon dioxide concentration is zero.)

**Minute volumes.**

Of these quantities, the expired minute volume is the simplest to measure. Many different anaesthetic gas circuits can be modified to permit collection of the expired gas in a Tissot spirometer or a Douglas bag. The measurement of the inspired minute volume of an anaesthetized patient, however, presents a considerable challenge. It is, of course, possible to construct a special gas circuit in which the patient breathes from one Tissot spirometer into another by means of unidirectional valves. However, this solution is clumsy (and expensive). In the absence of nitrogen equilibrium, we first considered adding a fixed concentration of an inert gas of low solubility to the inspired gas. We hoped that the body might rapidly attain equilibrium with a gas of very low solubility and that the ratio of the inspired and expired concentrations would enable us to derive the inspired minute volume from the more easily measured expired minute volume. One gas appears especially suitable for this purpose. Sulphur hexafluoride is biologically and chemically inert and has a water solubility only one-tenth that of helium. We were also able to demonstrate that the gas chromatograph (with a dimethyl sulphoxide stationary phase) would easily detect sulphur hexafluoride in the presence of nitrous oxide and the low thermal conductivity of the gas permitted its easy detection with a simple catharometer in concentrations of about 1 per cent. Unfortunately, sulphur hexafluoride is prepared for non-biological purposes and contains minute traces of SF₆, S₂F₁₀, both of which are highly toxic. The purification of the gas is exceedingly difficult and we considered that the commercial grade was unsuitable for inhalation by anaesthetized patients although it has been inhaled by conscious volunteers. Helium could be used as an alternative tracer gas for determination of the inspired/expired volume ratio but we were deterred by the difficulties of measurement of helium concentrations in the presence of oxygen, carbon dioxide, nitrous oxide and residual traces of nitrogen.

We next considered the possibility of using a pair of Wright respirometers—one to measure the inspired minute volume and the other the expired minute volume. Nunn and Ezi-Ashi (1962) have found that the response of the respirometer is influenced by temperature, gas composition, minute volume and respiratory waveform, all of which differ between inspiration and expiration. While the respirometer is adequate for the clinical monitoring of ventilation, it is hardly suitable for the measurement of the difference between inspired and expired minute volume, which has been found to be of the order of 5 to 10 per cent of the minute volume.

We were thus forced back to spirometry for the measurement of the two minute volumes. We have adapted the method of Donald and Christie (1949) and used a box-bag system in reverse. This is described in detail below.
Construction.

The box has been constructed from a 40-litre open-topped glass jar originally used for museum specimens. The top is sealed with a perspex plate cemented to the glass with "Evostik". All connections with the interior are made through a second perspex plate which is bolted over a hole in the first plate (fig. 1).

In the original box-bag described by Donald and Christie (1949) expired gas passed into the box. However, as we wished to collect and then to sample expired gas, it was found more convenient to cause the patient to breathe from the box into the bag, since the latter could be emptied before the collection period. The bag is a latex meteorological balloon of capacity greater than 40 litres, supplied by the Guide Bridge Rubber Company, Bury, Lancashire. Sampling manifolds are provided for both box and bag, and a mercury-in-glass thermometer is let into the box.

All passages carrying tidal flow of gas are of 2 cm internal diameter. The connections are as follows:

1. From the box to the patient via an inspiratory unidirectional valve.
2. From the patient to the bag via an expiratory unidirectional valve.
3. From the box to a spirometer of sensitivity 1 cm = 67 ml.

Box-bag, spirometer and kymograph are mounted on a trolley which can be brought close to the patient. Fresh gas is delivered from a conventional Boyle apparatus via a two-stage humidifier (at ambient temperature) to the box, which it enters through the sampling manifold.

Procedure.

Prior to the induction of anaesthesia, the bag is emptied and the box flushed out with the intended fresh gas mixture. The patient is then anaesthetized and, following intubation, is connected to the unidirectional valves of the box-bag system (fig. 1). The expiratory tubing at this stage is not connected to the bag, which is closed with a tap. The expired gas vents freely to atmosphere. Inspired gas is drawn from an excess flow of fresh gas from a Boyle apparatus which passes through the humidifier into the box. Surplus fresh gas flow vents to atmosphere from below the spirometer bell. Anaesthesia can be maintained for an indefinite period with this arrangement. The movement of the spirometer gives an indication of respiration which is adequate for the conduct of the anaesthetic but the circuit, as described, is suitable only for spontaneous

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**Fig. 1**

The circuit of the box-bag spirometer system. Connections are shown in the correct position for measurement of inspired and expired minute volume and for collection of expired gas.
respiration. The measurement/collection period can be started at any convenient time.

At the commencement of the measurement/collection period, the following changes in the circuit are made:

1. The fresh gas flow is stopped and the inlet to the box clamped.
2. The expired gas is diverted from atmosphere to the bag.

Figure 1 shows the connections to the bag during the collection/measurement period.

During the first hour of nitrous oxide anaesthesia the expired minute volume has always been less than the inspired minute volume and, therefore, the spirometer bell descends during the collection period, which is limited either by distension of the bag or by bottoming of the spirometer. It is usually possible to collect for at least 4 minutes.

During collection, respiration is recorded on the spirometer and it is thus possible to watch for changes in respiratory pattern and volume which might influence gaseous exchange. Box temperature is read to the nearest 0.1°C throughout the collection. At the end of the collection/measurement period, the endotracheal tube is disconnected from the unidirectional valve box and connected to the Boyle apparatus by way of a Magill attachment or other preferred gas circuit. The box-bag spirometer trolley is then wheeled out of the operating theatre into the laboratory for analysis of the gas mixtures. For certain studies, arterial blood is withdrawn during the collection period.

**Derivation of minute volumes.**

Figure 2 shows a typical spirometer trace. After correction for temperature changes, the

![Diagram]

**TEMP. CHANGE IN 3-5 MIN. = 0.2°C**

**VOL. CHANGE IN 3-5 MIN. = 46 ML**

\[ V_t = \sum V_t(\text{obs}) \text{ in 1 MIN} = 4500 \text{ ML/MIN} \]

\[ \Delta V = 248 \text{ ML/MIN} \]

\[ \bar{V}_t = \frac{V_t}{4} = 1125 \text{ ML/MIN} \]

\[ \Delta V = 261 \text{ ML/MIN} \]

\[ \bar{V}_t = 5148 \text{ ML/MIN} \]

**A typical record obtained with the apparatus shown in figure 1 showing method of calculation and correction for temperature change. It will be noted that the calculated inspired minute volume is independent of the temperature correction. The correction is, however, needed to calculate the true value of expired minute volume and the difference between inspired and expired minute volume. The trace during the pre-collection period is only qualitative and does not indicate the true ventilation.**
difference between inspired and expired volume is indicated by the slope of the trace. It should be stressed that the difference between the inspired and expired minute volume is the algebraic sum of the following:

- Oxygen uptake.
- Nitrous oxide uptake.
- Halothane uptake.
- Nitrogen output.
- Carbon dioxide output.

Therefore the oxygen uptake cannot be derived directly from the slope of the trace. This is in contrast to the closed circuit spirometer technique for measurement of oxygen consumption in which it is assumed that the observed change in volume comprises solely oxygen uptake. Under the conditions of nitrous oxide anaesthesia, the slope of the spirometer trace indicates no more than the difference between inspired and expired minute volume.

The measurement of the actual expired minute volume is much less critical than the measurement of the difference between inspired and expired minute volume. The expired minute volume may be conveniently determined as the sum of the expired tidal volumes on the trace, divided by the duration of collection.

It is fortunate that expired air cools, almost to ambient temperature, during passage through a 1-metre length of corrugated tubing. Temperature changes in the system are, therefore, small. For a rise of temperature from 20°C to 21°C, the change of volume in the system (46 litres) would be 230 ml (measured at ATPS). In fact, the largest temperature rise so far recorded during collection has been 0.2°C. This corresponds to a volume increase of 46 ml, or 13 ml/min during a 3½-minute collection (fig. 2). This must be subtracted from the expired minute volumes derived from the spirometer trace. It must also be added to the difference between expired and inspired minute volumes derived from the slope of the spirometer trace.

If the inspired gas were dry, expired air would carry about 2 per cent water vapour from the patient. This would markedly influence the inspired/expired minute volume difference. This complication has been avoided by saturating the inspired gas at ambient temperature. In addition to the humidifiers shown in figure 1, the floor of the box is kept awash with water.

All gas volumes are measured at ATPS. Correction may be made to STPD or BTPS as required. It is, therefore, necessary to record ambient temperature and pressure and the patient's temperature at the time of collection.

**Analysis of gases.**

Analysis of gases must be carried out as soon as possible to minimise the error due to diffusion through the wall of the bag (Nunn, 1958).

**Carbon dioxide.**

We elected to measure the expired gas carbon dioxide concentration by means of the carbon dioxide sensitive electrode since the apparatus was already available for the measurement of blood Pco₂. Fortunately the accuracy of the method is maximal at the low concentrations of carbon dioxide found in expired gas. The sensitivity of the electrode is checked daily between 100 per cent carbon dioxide and a mixture of approximately 3 per cent carbon dioxide in oxygen, which has previously been analyzed by Lloyd's modification of the Haldane apparatus (Lloyd, 1958). The latter gas mixture is also used as the standard with which the expired gas carbon dioxide concentration is compared. During anaesthesia we have seldom found the carbon dioxide concentration of the mixed expired gas to be outside the range 1.5 to 5.5 per cent; 3 per cent carbon dioxide is thus a suitable standard for analysis of expired gas. Samples of expired gas are analyzed in quadruplicate, each sample being preceded and followed by the standard gas. During analysis the electrode temperature is held constant to ±0.1°C. The electrode signal voltage is measured potentiometrically to 0.1 mV, using a Vibron electrometer as a null detector. Expired gas is sampled continuously from the bag by weighting the spirometer bell.

**Oxygen.**

The oxygen concentration of the inspired and expired gas is determined with a Clark polarographic electrode using a 60μ polyethylene membrane. Air is used as the calibrating gas since this is reasonably close to the expected inspired and expired oxygen concentrations. The blank reading of the electrode is determined with 100 per cent carbon dioxide which is already available for checking the
sensitivity of the carbon dioxide electrode. Gas samples are analyzed in quadruplicate, each sample being preceded and followed by air which is used as the standard. During analysis the electrode temperature is held constant to ±0.1 °C. The electrode signal (current) is backed off, using the circuit described by Severinghaus and Bradley (1958) but using the Vibron electrometer as a null indicator. Expired and inspired gas are sampled continuously from bag or box, by weighting the spirometer bell.

ASSESSMENT OF ACCURACY

Expired minute volume.

The accuracy of the measurement of minute volume, using the same spirometer, was assessed from data previously reported (Nunn, 1956). Up to a minute volume of 10 l./min and a respiratory frequency of 35 b.p.m. there was found to be no significant systematic error but a random error which was a function of the volume measured. The coefficient of variation (standard deviation of a measurement expressed as a percentage of the measurement) was 1.1 per cent. An error introduced into the measured expired minute volume results in a proportionate error in the calculated carbon dioxide output or oxygen uptake (table I).

Inspired/expired minute volume difference.

For determination of oxygen uptake, the accuracy of the measurement of the inspired/expired minute volume difference is more critical than the measurement of the actual expired minute volume. This is shown in the example (table I) which uses typical values and compares the error introduced into the calculated values for gas exchange when an error of +50 ml is introduced into:

1) both inspired and expired minute volume;
2) the difference between inspired and expired minute volume.

| Table I |
|----------------------------------|----------------|----------------|----------------|----------------|
| Effect of error of +50 ml in measurement of gas volumes on calculated values for gas exchange. |
| $V_1$ (ml) | $V_E$ (ml) | $F_{O_2}$ | $F_{E_{O_2}}$ | $F_{E_{CO_2}}$ | $V_{CO_2}$ (ml) | $V_{O_2}$ (ml) | $R$ |
| $V_1$ and $V_E$ correct | 5250 | 5000 | 0.3000 | 0.2500 | 0.0400 | 200 | 325 | 0.615 |
| $V_1$ and $V_E$ both in error by +50 ml | 5300 | 5050 | 0.3000 | 0.2500 | 0.0400 | 202 | 328 | 0.616 |
| $V_E$ correct but $\Delta V$ in error by +50 ml | 5300 | 5000 | 0.3000 | 0.2500 | 0.0400 | 200 | 340 | 0.588 |

It is difficult to assess the accuracy of the measurement of the inspired/expired minute volume difference. Substitution of a pump for the patient resulted in no significant volume change of the box-bag-spirometer system, other than that due to temperature changes. During anaesthesia, respiration is usually sufficiently regular for the fitting of a satisfactory line through the end expiratory levels recorded on the kymograph (fig. 2) and actual volume changes can be read to within ±2 per cent. Probably a more important source of error is a temperature change which is not adequately shown by the thermometer. However, it is most unlikely that expired air can enter the bag at more than 0.2°C above ambient temperature, with which the box has ample time to equilibrate before the collection period. Taking into account the magnitude of those factors, the inspired/expired minute volume difference can probably be measured with an error whose coefficient of variation is less than 2 per cent, or whose standard deviation is less than 10 ml, whichever is the greater.

Carbon dioxide output.

The accuracy of the carbon dioxide sensitive electrode as a gas analyzer was assessed by comparison with the analyses of a series of gas mixtures by the Lloyd-Haldane apparatus (table II). Each measurement is the result of a single analysis and no results have been excluded.

The mean error is not significant and no allowance has been made for any systematic error. During a clinical study, the carbon dioxide concentration of a gas mixture has always been determined as the mean of four analyses. Under these circumstances the coefficient of variation of the error would be reduced by the square root of four—to 0.27 per cent. Thus, a carbon dioxide concentration of 3.000 would be measured with 95 per cent confidence limits of 2.985 to 3.015. This degree of accuracy is similar to that custom-
arily ascribed to the Haldane or Scholander technique. Our method, therefore, appears to be limited by the chemical analysis of the standard gas mixture.

Since the carbon dioxide output is measured as the product of VE and FE CO₂, the coefficient of variation of its error (the square root of the sum of the squares of the coefficients of variations of the errors in measurement of VE and FE CO₂) is 1.1 per cent. Thus for a typical measured carbon dioxide output of 150 ml the 95 per cent confidence limits of the measurement would be 147 to 153 ml/min.

Oxygen uptake.

The accuracy of the polarograph as a gas analyzer was assessed by comparison with the analyses of a series of gas mixtures by the Lloyd-Haldane or Scholander apparatus (table II). Each measurement is the result of a single analysis and no results have been excluded. It has been established that the polarograph does not respond to nitrous oxide.

The mean error in table II is not significant and no allowance had been made for any systematic error. During a clinical study, the oxygen concentration has always been determined as the mean of four analyses. Under these circumstances the coefficient of variation of the error would be reduced to 0.61 per cent. Thus an oxygen concentration of 25 per cent would be measured with 95 per cent confidence limits of 24.7 to 25.3 per cent. This level of accuracy is considerably less than that obtainable with the Haldane or Scholander apparatus and is the principal factor limiting the accuracy of the measurement of oxygen uptake during anaesthesia.

In terms of the quantities actually measured, the oxygen uptake may be expressed as follows:

\[
\dot{V}_E \left( 1 + \frac{\Delta V}{\dot{V}_E} \right) F_{1O_2} - F_{E O_2}
\]

\(\dot{V}_E\) is taken outside the bracket since error in \(\dot{V}_E\) introduces only a proportionate error into the calculated \(\dot{V}_{O_2}\) (table I). The error in \(\frac{\Delta V}{\dot{V}_E}\) is maximal when \(\Delta V\) is large and \(\dot{V}_E\) is small. After 20 minutes of nitrous oxide anaesthesia we have usually found \(\Delta V\) to be less than 250 ml/min which accords with the values for nitrous oxide uptake reported by Severinghaus (1954).

We shall therefore calculate the error in \(\frac{\Delta V}{\dot{V}_E}\) when \(\Delta V\) is 250 ml/min and \(\dot{V}_E\) is 3 l/min which is the lowest minute volume which the authors believe to be compatible with satisfactory anaesthesia. Under these conditions, the standard deviation of \(\frac{\Delta V}{\dot{V}_E}\) and \(\left( 1 + \frac{\Delta V}{\dot{V}_E} \right)\) is 0.344 and the coefficient of variation of \(\left( 1 + \frac{\Delta V}{\dot{V}_E} \right)\) is 0.318 per cent. The coefficient of variation of \(\frac{\Delta V}{\dot{V}_E}\) is 0.69 per cent compared with 0.61 per cent for \(F_{E O_2}\). The next stage in the calculation of the error in \(\dot{V}_{O_2}\) requires determination of the standard deviation of the error in measurement of these two quantities. This is possible only in relation to assumed numerical values for \(\Delta V\) for \(\dot{V}_{O_2}\), \(\dot{V}_T\) and \(F_{1O_2}\). Assuming a value of 250 ml/min for \(\Delta V\) and 200 ml/min for \(\dot{V}_{O_2}\), table III shows the coefficient of variation for measured \(\dot{V}_{O_2}\) at various values of \(\dot{V}_T\) and \(F_{1O_2}\). The standard deviation of the error in measured \(\dot{V}_{O_2}\) approximates to 0.8 per cent of the total inspired oxygen (\(\dot{V}_T \times F_{1O_2}\)).

### Table II

Accuracy of the electrodes for measurement of oxygen and carbon dioxide concentrations in gas mixtures (comparison with Lloyd-Haldane apparatus).

<table>
<thead>
<tr>
<th></th>
<th>Carbon dioxide</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of analyses</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Range of concentrations studied</td>
<td>2.8–9.9%</td>
<td>7.5–34%</td>
</tr>
<tr>
<td>Mean error expressed as a percentage of the concentration of the gas</td>
<td>+0.19%</td>
<td>-0.38%</td>
</tr>
<tr>
<td>Coefficient of variation of the error</td>
<td>0.54%</td>
<td>1.22%</td>
</tr>
<tr>
<td>Standard error of the mean error</td>
<td>0.12%</td>
<td>0.26%</td>
</tr>
</tbody>
</table>

### Table III

SD of error of measured \(\dot{V}_{O_2}\) assuming \(\Delta V\) is 250 ml/min and \(\dot{V}_{O_2}\) is 200 ml/min. SD in ml/min.

<table>
<thead>
<tr>
<th>Expired volume (l)</th>
<th>(F_{1O_2}) 20%</th>
<th>(F_{1O_2}) 30%</th>
<th>(F_{1O_2}) 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>5.8</td>
<td>8.6</td>
<td>14.4</td>
</tr>
<tr>
<td>5.0</td>
<td>9.2</td>
<td>13.0</td>
<td>23.4</td>
</tr>
<tr>
<td>10.0</td>
<td>18.4</td>
<td>28.8</td>
<td>48.8</td>
</tr>
</tbody>
</table>
Moderate variations in $\Delta V$ and $\dot{V}_O_2$ have negligible effect on the error.

**Respiratory exchange ratio.**

The error in the measurement of the respiratory exchange ratio is dependent upon the error in both carbon dioxide output and oxygen uptake. Since the latter is considerably larger than the former, it is correspondingly more important. The error in the measurement of the carbon dioxide output is a function of the carbon dioxide output itself and is best considered as a coefficient of variation. However, the error in the measurement of the oxygen uptake is neither constant nor is it a function of the oxygen uptake. Its value is dependent upon a number of factors (table III) and must be assessed for each particular case. The coefficient of variation of the error in the measured respiratory exchange ratio is the square root of the sum of the squares of the coefficients of variation of the error in the measured carbon dioxide output and oxygen uptake, and so must also be determined for each particular case. For example, when $\dot{V}_O_2$ is 200 ml/min, $V_1$ is 5,250 ml/min, $V_E$ is 5,000 ml/min and $F_{I_0}$ is 0.3000, the coefficient of variation of the error in the measured respiratory exchange ratio is 6.8 per cent. Thus, with a measured $R$ of 0.80, the 95 per cent confidence limits are 0.69 to 0.91.

**Diffusion through the wall of the bag.**

The passage of individual constituent gases through the wall of the bag depends upon the following factors:
- permeability of rubber and thickness of wall of bag;
- permeability factor of individual gases;
- partial pressure gradients of each constituent gas across the wall of the bag;
- ratio of volume of gas sample to surface area of bag.

Typical conditions at the end of our collection periods are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Bag</th>
<th>Box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (litres)</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Oxygen (per cent)</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Carbon dioxide (per cent)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nitrous oxide (per cent)</td>
<td>71</td>
<td>70</td>
</tr>
</tbody>
</table>

Under these conditions the carbon dioxide concentration in the bag falls at about 0.005%/min while the oxygen concentration rises at about 0.012%/min. A correction is applied according to the time elapsed between collection and analysis.

**Applications**

**Carbon dioxide output.**

Provided that the inspired carbon dioxide concentration is zero, the output may be measured easily by collection of expired gas. The box-bag technique is therefore unnecessary for this measurement. However, if there is an appreciable inspired concentration of carbon dioxide, the output (or uptake) can be determined only by measurement and analysis of both inspired and expired gas. The system described would be suitable for this purpose.

**Oxygen uptake.**

The measurement of oxygen uptake during nitrous oxide anaesthesia is important since the oxygen consumption is the major factor determining the ventilation and inspired oxygen concentration which are required.

Either oxygen uptake or carbon dioxide output may be used for measurement of the cardiac output by application of the direct Fick principle. Apart from the difficulty of sampling and measuring the blood gas concentrations, there are two sources of error related to the measurement of the gaseous exchange. Firstly, there is the error in the measurement of the oxygen consumption discussed above. The error induced in the cardiac output will be proportional to the error in the measured oxygen. Thus, using the box-bag system, with the example quoted above, the error attributable to the measurement of oxygen uptake, induced into a direct oxygen Fick determination of cardiac output would have a coefficient of variation of 6.7 per cent. A second source of error has been brought to our notice by Dr. J. P. Payne. If, during the collection period, the alveolar oxygen concentration changes (most likely in association with a change in carbon dioxide concentration) there will be a discrepancy between the oxygen uptake (measured at the mouth) and the amount of oxygen which has crossed the alveolar-capillary membrane and so figures in the Fick equation. If the functional residual capacity is 3 litres and the alveolar $P_{O_2}$ changes by 5 mm Hg/min, the discrepancy will amount to 20 ml/min which is 10 per cent of the expected oxygen consumption.
Respiratory exchange ratio.

Such evidence as is available suggests that the metabolic respiratory exchange ratio approximates to the normal value of 0.82 during anaesthesia (Nunn and Matthews, 1959). Departures from this figure are useful indications of an unsteady respiratory state.

The respiratory exchange ratio is conveniently used to define the relationship between alveolar Po\(_2\), inspired gas Po\(_2\) and alveolar Pco\(_2\):

\[
P_{\text{A}O_2} = P_{\text{I}O_2} - \frac{P_{\text{A}CO_2}}{R} (1 - F_{\text{I}O_2} (1 - R))
\]

(after Rossier and Mean, 1943) ...(v)

In its more elaborate form:

\[
P_{\text{A}O_2} = P_{\text{I}O_2} - \frac{P_{\text{A}CO_2}}{R} \left[ 1 - F_{\text{I}O_2} (1 - R) \right]
\]

(Fenn, Rahn and Otis, 1946), it is the basis of the indirect determination of the ideal alveolar Po\(_2\). The difference between the calculated ideal alveolar Po\(_2\) and the measured arterial Po\(_2\) is a valuable method of determination of diffusing capacity, maldistribution and shunts. The measurement of the respiratory exchange ratio is thus of great importance in the measurement of these variables. It is therefore important to know whether R may be measured with sufficient accuracy for the calculation of P\(_{\text{A}O_2}\). It has been shown above that, using the box-bag technique, under typical circumstances, R can be measured with a coefficient of variation of 6.8 per cent. This is comparable with the figure of 4 per cent which is the coefficient of variation of the error in our measurement of blood Pco\(_2\) (unpublished). With Pco\(_2\)=40 mm Hg, and R=0.8 the 95 per cent confidence limits of Pco\(_2\)/R would be 42.1 to 57.9 mm Hg, a range which is again comparable with that due to the error in measured arterial blood Po\(_2\) (coefficient of variation of 5 per cent, unpublished). When the arterial Po\(_2\) is about 100 mm Hg, it follows that the alveolar-to-arterial Po\(_2\) difference can be measured by this technique with a standard deviation of 6.4 mm Hg compared with a mean value of about 4 mm Hg using conventional methods (Campbell, Nunn and Peckett, 1958).

The respiratory exchange ratio is not solely of academic interest. It is well known that patients seldom attain a steady respiratory state during anaesthesia, but we have repeatedly been surprised how low the respiratory exchange ratio may be as long as 20 minutes after the start of what appears to be a normal anaesthetic. We have, for example, recorded the following data in a woman of 49 years, undergoing stripping of varicose veins, after 15 minutes of nitrous oxide, oxygen and halothane anaesthesia, with an inspired oxygen concentration of 29.3 per cent. They are illustrative of the information obtainable from simultaneous analysis of arterial blood, inspired and expired gas.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon dioxide output</td>
<td>61 ml/min STPD</td>
</tr>
<tr>
<td>Oxygen uptake</td>
<td>174 ml/min STPD</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean minute volume</td>
<td>3.20 l./min BTPS</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>123 ml BTPS</td>
</tr>
<tr>
<td>Respiratory frequency</td>
<td>26 BPM</td>
</tr>
<tr>
<td>Apparatus deadspace</td>
<td>34 ml</td>
</tr>
<tr>
<td>Personal physiological deadspace</td>
<td>55 ml BTPS = 45% of tidal volume</td>
</tr>
<tr>
<td>Alveolar ventilation</td>
<td>880 ml/min BTPS</td>
</tr>
<tr>
<td>Measured arterial Pco(_2)</td>
<td>62.7 mm Hg</td>
</tr>
<tr>
<td>Measured arterial Po(_2)</td>
<td>57.4 mm Hg</td>
</tr>
<tr>
<td>Calculated arterial saturation</td>
<td>85%</td>
</tr>
<tr>
<td>Calculated alveolar Po(_2)</td>
<td>63.0 mm Hg</td>
</tr>
<tr>
<td>Alveolar to arterial Po(_2) difference</td>
<td>5.6 mm Hg</td>
</tr>
</tbody>
</table>

At an alveolar Po\(_2\) of 63 mm Hg, either an impaired diffusing capacity or an abnormal shunt effect would have resulted in an increased alveolar-to-arterial Po\(_2\) difference. In fact the difference was well within the normal range. We may therefore conclude that the arterial hypoxia was not due primarily either to an impaired diffusing capacity or to abnormal shunting.

The next consideration is ventilation, and the low alveolar Po\(_2\) in the presence of a high inspired oxygen concentration suggests that the hypoxia resulted from underventilation. Nevertheless the arterial Pco\(_2\) was only 62.7 mm Hg—a level which is commonplace during anaesthesia and not usually associated with hypoxia when the inspired oxygen is as high as 30 per cent. However, in this patient, the striking feature was the respiratory exchange ratio of 0.35. This indicated that the patient was seriously underventilating and was still far from being in a steady state. The arterial Pco\(_2\) was thus still rising and, assuming that the

\*
The alveolar air equation may be rearranged without R, but it then contains Vo\(_2\) and Va. The problems of measurement are thus unchanged.
ventilation and metabolic activity were maintained, and that the metabolic exchange ratio was 0.8, we may predict that the arterial $P_{\text{CO}_2}$ would eventually have risen to 143 mm Hg. The patient's ventilatory state was thus far worse than was apparent from the measured arterial $P_{\text{CO}_2}$, which gave no indication that she had not reached a steady state. The same problem may be expressed differently in terms of the relative rate at which oxygen and carbon dioxide reach a steady state. Farhi and Rahn (1955) have suggested that, following a step change of ventilation, oxygen reaches its new level about eight times faster than carbon dioxide. Thus, in the example quoted above, the arterial oxygen tension had already reached the low level determined by the under-ventilation while the arterial carbon dioxide tension was still slowly mounting to its new elevated level. The true state of the ventilation could therefore only be assessed from the arterial $P_{\text{CO}_2}$ in relation to the respiratory exchange ratio. The extreme example is apnoea after breathing air. Arterial hypoxia develops rapidly but the arterial $P_{\text{CO}_2}$ can rise by only about 4 mm Hg per min (Frumin et al., 1959). The patient may thus die of hypoxia caused by underventilation although the $P_{\text{CO}_2}$ is only 60 mm Hg. However, during this period the respiratory exchange ratio is zero, indicating a grossly unsteady state.

Such a case affords a striking demonstration of the importance of considering the expiratory exchange ratio as well as the arterial $P_{\text{CO}_2}$ when assessing ventilation. Nevertheless, it is for the study of the other causes of hypoxia that the measurement of the respiratory exchange ratio is likely to prove more useful. Our limited experience of the wide range of respiratory exchange ratios encountered during anaesthesia suggests that its measurement is essential to the calculation of the ideal alveolar $P_{\text{O}_2}$. An exception occurs when the inhaled oxygen concentration approximates to 100 per cent. Under these circumstances $R$ cancels from equation (vi) and this is fortunate as the measurement of the oxygen uptake is subject to a large error when the inhaled oxygen concentration is high (table III).

The difference between the calculated ideal alveolar $P_{\text{O}_2}$ and the measured arterial $P_{\text{O}_2}$ is dependent upon different aspects of pulmonary physiology according to the actual level of the alveolar $P_{\text{O}_2}$. Thus at levels up to about 50 mm Hg, the difference is almost entirely a function of diffusion and may be used for the estimation of the oxygen diffusing capacity. As the alveolar $P_{\text{O}_2}$ rises, the influence of diffusion decreases and that of admixture with venous blood increases until, above an alveolar $P_{\text{O}_2}$ of 90 mm Hg, the effect of diffusing capacity is usually negligible and the difference may be used for the estimation of venous admixture. This admixture consists of two parts: frank shunting (as, for example, through underventilated alveoli) and maldistribution (blood flow through relatively underventilated alveoli). If the arterial $P_{\text{O}_2}$ is above about 200 mm Hg, the effect of maldistribution is overcome by the raising of the $P_{\text{O}_2}$ in even the worst ventilated alveoli. The alveolar-to-arterial $P_{\text{O}_2}$ difference is then an indication of true shunts. Thus by studying the difference at three levels of oxygenation it is possible to gain information on diffusing capacity, maldistribution and shunts—all factors of considerable clinical significance in the oxygenation of the anaesthetized patient.

Nitrous oxide exchange.

We have stated above that the change in volume of the box-bag-spirometer system indicates the algebraic sum of:

- Oxygen uptake.
- Nitrous oxide uptake.
- Halothane uptake.
- Nitrogen output.
- Carbon dioxide output.

The values for oxygen and carbon dioxide exchange may be determined when the inspired and expired gases have been analyzed. Halothane uptake and nitrogen output can be roughly estimated and the remainder is nitrous oxide uptake. This application of the box-bag was pointed out by Donald and Christie (1948). The values which we have so far obtained are in accord with the data on nitrous oxide uptake reported by Severinghaus (1954).

ADDENDUM

Recent studies in San Francisco (Staub, personal communication) suggest that the diffusion component of the alveolar-arterial $P_{\text{O}_2}$ gradient is much smaller than has hitherto been thought. It
now appears likely that the total gradient consists of two main components due to shunt and maldistribution, both of which constitute “venous admixture”.

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