Recent advances in gas exchange measurement in intensive care patients

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Adequate resuscitation, shock reversal, and prevention of organ failure are central to modern intensive care. Shock is frequently defined as the presence of insufficient oxygen supply to tissues to meet metabolic demands. The measurement of oxygen consumption by critically ill patients is potentially useful, because it indicates the net result of oxygen delivery to the tissues and the ability of cells in the tissues to use oxygen. Assessment of carbon dioxide elimination can provide information about respiratory physiology and, when combined with oxygen consumption, energy expenditure and metabolism. It has been recognized for many years that oxygen delivery and utilization are often abnormal in many types of critical illness. Despite these observations the relevant literature is confusing and contradictory. One reason for this is misunderstanding of the methodological limitations of techniques for assessing gas exchange. This article reviews key methodological issues relating to gas exchange measurement in the ICU, some currently available devices, and the potential value of these measurements in the management of the critically ill patient.

Historical perspective
Interest in gas exchange measurement in the critically ill came from two fields of physiological and clinical research: assessment of nutrition and the study of oxygen kinetics during critical illness.

Nutrition
The principle of direct calorimetry has been established for 200 yr. This states that the energy content of foods can be determined by measuring the heat released during combustion. Combustion requires oxygen and generates carbon dioxide. It was recognized by Benedict and Atwater in the early 20th century that energy expenditure in humans could be determined if oxygen consumption and carbon dioxide elimination are measured accurately, particularly if nitrogen balance is also calculated. This method was termed indirect calorimetry. It is the accepted method for measuring energy expenditure and substrate utilization in humans. Devices for assessing gas exchange are often called indirect calorimeters. Critical illness results in catabolism and the inability to ingest foods normally. The introduction of parenteral and enteral nutrition led to interest in measuring energy expenditure to determine the dose of nutrition required and the metabolic effects associated with artificial nutrition. Early techniques were laborious and inaccurate because of the technical problems of measurements in mechanically ventilated patients. Despite these limitations it became clear that underfeeding increased catabolism and that overfeeding was associated with hyperglycaemia, increased ventilation requirements, and lipogenesis. These potentially adverse outcomes led to commercial interest in developing automated monitors to measure energy expenditure.

Oxygen kinetics
Cardiac output (CO) measurements in critically ill patients became widely used with the introduction of the pulmonary artery catheter (PA catheter). It was recognized that the Fick principle, originally used to determine CO from measurement of oxygen uptake and blood samples to estimate the arteriovenous oxygen content difference, could be modified to determine oxygen consumption if CO could be measured by thermodilution. This was termed the inverse or reverse Fick method. Calculations made using the physiological values obtained from a PA catheter included both oxygen delivery ($D_{O_2}$) and oxygen consumption ($V_{O_2}$):

$$D_{O_2} = CO \times (arterial\ oxygen\ content)$$
$$V_{O_2} = CO \times (arterial\ oxygen\ content - mixed\ venous\ oxygen\ content).$$
Until recently, it was widely believed that inadequate $D_O_2$ and tissue hypoxia were the principal causes of multiple organ failure during critical illness. This led to studies of oxygen kinetics using measurements made from PA catheters, and the widespread use of oxygen transport variables in the management of the critically ill. The literature in this area before 1990 is contradictory and confusing, in part because methodological issues, which are discussed below, confounded many studies. When indirect calorimeters were developed with sufficient accuracy for measuring $V_O_2$ from ventilator gases in mechanically ventilated patients, these devices were adapted for oxygen kinetics studies. These studies have clarified many issues relating to oxygen transport during critical illness.

### Determinants of metabolic gas exchange in the critically ill

**Oxygen consumption**

Under aerobic conditions $V_O_2$ is determined by the metabolic activity of tissues. The amount of oxygen needed to produce 1 kcal of energy from carbohydrate is 207 ml, from fat 213 ml, and from protein 223 ml. During critical illness many factors can alter metabolic rate and influence $V_O_2$ (Table 1). As a result $V_O_2$ can change rapidly and considerably during routine management (Fig. 1). The body does not contain significant stores of oxygen. The majority is bound to haemoglobin within red cells and amounts to about 1 l in a healthy 70 kg male. In health, normal resting $D_O_2$ is about 1000 ml min$^{-1}$ and $V_O_2$ is 250 ml min$^{-1}$, resulting in a resting oxygen extraction ratio (OER) of 25%. If oxygen demand increases or $D_O_2$ decreases, an imbalance in the supply–demand relationship can result in tissue hypoxia if the OER cannot increase sufficiently to match demands. The value of the critical oxygen delivery ($D_O_2$.crit) and critical oxygen extraction ratio (OER.crit), both at a whole body and regional level, is of considerable interest in the ICU. Tissue hypoxia, either because $D_O_2$ is inadequate or because the cells do not use oxygen normally, is probably the cause of organ failure in critical illness. Early literature suggested that the $D_O_2$.crit was substantially increased during critical illness, but recent work indicates that the increase is more modest on a whole body level. A study of septic and non-septic ICU patients during progressive reduction in $D_O_2$ as part of terminal care found a $D_O_2$.crit of approximately 4 ml kg$^{-1}$ min$^{-1}$ and OER.crit of approximately 0.6.

### Carbon dioxide elimination

Carbon dioxide is generated by aerobic metabolism, it is also found during anaerobic metabolism because hydrogen ions, associated with lactic acid production, are buffered to form carbon dioxide. Under aerobic conditions production of 1 kcal of energy produces 207 ml carbon dioxide from carbohydrate, from fat 151 ml, and from protein 181 ml. Body stores and transport of carbon dioxide within the body are complex; the total body store in a resting healthy 70 kg male is approximately 120 l. In steady-state carbon dioxide elimination ($V_CO_2$) from the lungs reflects metabolic production by tissues, and is normally approximately 200 ml min$^{-1}$. Changes can result from many factors, such as acute changes in ventilation, perfusion or acid–base status.
The time taken to re-establish steady state after a change is difficult to predict in practice, but can be as long as 30–60 min. Most of this process is completed in the initial minutes because it is a multi-exponential process. Unsteady state is particularly relevant to gas exchange methods because it is a potential source of error when \( V_O_2 \) measurement is based on the Haldane transformation (see below).

Carbon dioxide elimination can be described by the Bohr equation:

\[
\dot{V}_{CO_2} = \dot{V}_A \times P_{aCO_2} \times k
\]

where \( k \) is a constant that depends on the units used for each variable, and \( \dot{V}_A \) is alveolar ventilation. The relationship between \( \dot{V}_A \), the minute ventilation (\( \dot{V}_E \)), and the deadspace to tidal volume ratio (\( V_D/V_T \)) can be described by:

\[
\dot{V}_A = \dot{V}_E \times (1 - V_D/V_T).
\]

Combining these equations gives:

\[
\dot{V}_{CO_2} = \dot{V}_E \times (1 - V_D/V_T) \times P_{aCO_2} \times k.
\]

This equation shows that changes of minute ventilation, deadspace or arterial carbon dioxide concentration will affect carbon dioxide steady state and changes the \( \dot{V}_{CO_2} \) until the body pool stabilizes. In the ICU changes to steady state can occur frequently because of patient instability, particularly acute cardiorespiratory changes. In this clinical setting, the only practical method of assessing steady state is to examine continuous data.

**Respiratory quotient (RQ)**

The ratio between \( \dot{V}_{CO_2} \) and \( \dot{V}_{O_2} \) associated with metabolism at cellular level is called the RQ:

\[
RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}.
\]

Gas exchange measurements made with metabolic monitors are only identical to the cellular RQ when oxygen and carbon dioxide stores are in steady state. Gas exchange measurements are often termed the respiratory exchange ratio, because values are strongly influenced by ventilation and pulmonary blood flow.

If a patient is in a steady state, respiratory exchange ratio will be the same as RQ and the value gives useful information about substrate use in the body. Under normal conditions RQ varies between 0.70 and 1.00. Commonly quoted RQ values for carbohydrate, fat and protein, and the gas volumes associated with metabolism are summarized in Table 2. It is possible to use urea nitrogen measurements to calculate a ‘non-protein RQ’. This method is beyond the scope of this review, but is described elsewhere. Non-protein RQ calculations are useful in assessing the ratio of carbohydrate to fat oxidation, because non-protein RQ changes linearly from 0.71 to 1.00 as the carbohydrate/fat oxidation ratio ranges from 0 to 100%.

If RQ measurement is greater than 1.00 or less than 0.70 it is first important to exclude an unsteady state, for example acute changes in ventilation or venous return. The most common reason for a high RQ in a ventilated patient is an increase in ventilation, and a low RQ a decrease in ventilation. Altered perfusion changes the RQ until steady state is re-established. Reduced venous return decreases carbon dioxide elimination by the lungs and can increase the respiratory exchange ratio, whereas increased perfusion can decrease RQ. Changes in RQ are also influenced by replenishment of oxygen debt. If steady state is present a value greater than 1.00 probably indicates lipogenesis from glucose or protein. This is rarely seen, but usually indicates excessive carbohydrate feeding; values greater than 1.3 should not occur. A value less than 0.70 may be caused by gluconeogenesis or ketone metabolism. Accurate assessment of these patterns requires calculation of non-protein RQ.

**Energy expenditure**

Energy expenditure can be calculated from gas exchange measurements assuming that energy production is principally aerobic and the patient is in steady state. The most accurate method includes urinary urea nitrogen and the Weir formula is widely used. Energy expenditure (kcal day\(^{-1}\)) = (5.50\(\times\dot{V}_{O_2}\)) + (1.76\(\times\dot{V}_{CO_2}\)) – (1.99\(\times\)urinary urea nitrogen).

In practice, protein oxidation occurs within relatively narrow physiological limits and contributes a small amount to total energy expenditure even during catabolism. Urea nitrogen is often impractical to determine during critical illness because renal failure may be present or does not accurately reflect protein excretion because liver function is impaired. It can be ignored or estimated without introducing clinically important errors to the estimated energy expenditure. Indirect calorimetry measurements of energy expenditure therefore rely on accurate measurement of \( \dot{V}_{O_2} \) and \( \dot{V}_{CO_2} \).

Energy expenditure can be estimated from predictive equations based on patient weight, height, age and sex. The most commonly used equations are the Harris–Benedict and Schofield formulae. Neither is designed specifically for use in the critically ill and assumptions are made to adjust for illness severity, temperature or infection. It is also

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Gas volume equivalent of 1 g of substrate (ml)</th>
<th>Caloric value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>830</td>
<td>1.00</td>
</tr>
<tr>
<td>Fat</td>
<td>2020</td>
<td>0.71</td>
</tr>
<tr>
<td>Protein</td>
<td>970</td>
<td>0.81</td>
</tr>
<tr>
<td>Urea nitrogen*</td>
<td>6040</td>
<td>27.0</td>
</tr>
</tbody>
</table>

*Urea nitrogen values are quoted because these are used in assessment of substrate utilization in clinical practice.
Methods of measuring gas exchange in the critically ill

The inverse Fick method

Calculation of $\dot{V}_O_2$ from the inverse Fick method is straightforward in patients with a PA catheter in situ:

$$\dot{V}_O_2 = CO \times (Hb \cdot S_{O_2} \cdot k_1 + P_{A_{O_2}} \cdot k_2) - (Hb \cdot S_{vO_2} \cdot k_1 + P_{vO_2} \cdot k_2).$$

CO is measured by thermodilution, and samples are drawn simultaneously from a systemic arterial catheter and pulmonary artery lumen of the PA catheter. Accurate measurement of oxygen content for arterial and mixed venous blood is best done by direct measurement, but these devices are not routinely available in the ICU. Calculation of oxygen content from haemoglobin concentration, haemoglobin oxygen saturation ($S_{O_2}$), oxygen partial pressure ($P_{O_2}$), and physiological constants for oxygen combining capacity with haemoglobin ($k_1$) and solubility ($k_2$) is automatic in modern blood gas analysers.

Calculation of $\dot{V}_{CO}$ is theoretically possible if carbon dioxide content can be determined, but this is impractical for routine use because carbon dioxide content cannot be measured or calculated accurately from routinely available measurements. The inverse Fick method is therefore used only to estimate $\dot{V}_{O_2}$.

The theoretical basis for $\dot{V}_{O_2}$ determination in the ICU using the Fick principle is physiologically correct except when intracardiac shunts are present. In addition, $\dot{V}_{O_2}$ by the lungs is excluded. However, there are problems associated with this method in the critically ill which result from two types of error, which have caused confusion in the literature. The first concerns the accuracy of individual measurements and the factors influencing this. The second concerns mathematical coupling when the method is used to explore changes in $D_{O_2}$ and $\dot{V}_{O_2}$.

Factors limiting the accuracy of inverse Fick calculations

It is clear from the above equation that many measurements are necessary to calculate $\dot{V}_{O_2}$. If all measurements had zero error then values calculated by the inverse Fick method would be accurate and reproducible, but this is not the case. All clinical measurements, particularly in critically ill patients, have an associated measurement error. In experimental or clinical studies, attempts may be taken to reduce error by minimizing delays in analysis, calibrating analysers carefully, using experienced technicians or investigators, or averaging repeated measurements. During clinical management larger measurement errors are likely because these steps are rarely used routinely. For example, CO measurement by bolus thermodilution has a frequently quoted accuracy of $\pm 10\%$. A particular problem is that errors in CO measurement are non-linearly related to the actual CO value. Measurement errors are greater at very high and low physiological values; these are often present in patients in whom measurements are made. Measurement of oxygen partial pressure is accurate with modern machines, but oxygen saturation measurement is problematic with some machines. This is particularly true for $S_{vO_2}$ because the value lies on the steep portion of the oxygen–haemoglobin dissociation curve, and is also subject to changes if analysis is delayed. Calculation of oxygen saturation, rather than direct co-oximeter measurement, can introduce large errors. Under controlled conditions, haemoglobin measurements by co-oximeters show good agreement with gold standard methods, but accuracy in the ICU setting may be less if incomplete sample mixing is present or machine calibration procedures are poorly followed.

In the inverse Fick calculation these errors are not simply added, as has frequently been stated, but are propagated in the final calculation. This is particularly true when the arterio-venous oxygen content difference is small and the CO is large, as is often the case in sepsis. Under these conditions large overall errors can occur in the $\dot{V}_{O_2}$ calculation despite relatively modest individual measurement errors. This phenomenon is illustrated in Table 3, and has been considered in detail elsewhere. The inverse Fick method therefore has an uncertain accuracy and reproducibility in the critically ill patient that depends on many factors (Table 4). This is rarely assessed either in clinical studies or clinical management, because intermittent ‘snapshot’ calculations are usually made.

A further factor that is rarely considered is the value for the combining capacity for haemoglobin with oxygen ($k_1$ in the equation above). The value for $k_1$ is variously quoted from 1.31 to 1.39 ml$^{-1}$ O$_2$ gHb$^{-1}$; the calculated value for arterio-venous oxygen content difference can differ by about 5% depending on which value is chosen in the calculation.

Mathematical coupling

When oxygen kinetics are assessed by calculating $D_{O_2}$ and $\dot{V}_{O_2}$ from PA catheter-based measurements a mathematical linkage can occur that gives the false impression that $D_{O_2}$ and $\dot{V}_{O_2}$ are positively correlated physiologically. This phenomenon has been considered in detail elsewhere, and has been a source of confusion in assessing the relationship between $D_{O_2}$ and $\dot{V}_{O_2}$ in the critically ill. A brief description is included here.

CO and arterial oxygen content are used to calculate both $D_{O_2}$ and $\dot{V}_{O_2}$ in calculations of oxygen kinetics. If these values could be obtained without any associated measurement error this would not be problematic in $D_{O_2}/\dot{V}_{O_2}$ studies, but as has been discussed above this is usually not the case. When large measurement errors are present there will be a mathematical linkage error. This has been illustrated by using random number tables to generate pairs of data that
Table 3 Illustration of error propagation with the inverse Fick method of calculating VO₂ under normal and hyperdynamic haemodynamic patterns. The true value represents the true physiological value and the measured value represents the clinical measurement with associated error. The percent errors for each of the primary measurements are set to be similar to those encountered in clinical practice. *Primary clinical measurement: all other variables are derived. The errors in primary measurements are set to be similar for both examples.

<table>
<thead>
<tr>
<th>Normal haemodynamic pattern</th>
<th>True value</th>
<th>Measured value</th>
<th>% Error</th>
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<tbody>
<tr>
<td>SaO₂ (%)*</td>
<td>98</td>
<td>97</td>
<td>1.0</td>
</tr>
<tr>
<td>SvO₂ (%)*</td>
<td>67</td>
<td>67.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Haemoglobin concentration (g litre⁻¹)</td>
<td>12</td>
<td>12.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Arterial O₂ content (ml dl⁻¹)</td>
<td>15.8</td>
<td>16.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Venous O₂ content (ml dl⁻¹)</td>
<td>10.8</td>
<td>11.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Arterio-venous difference (ml dl⁻¹)</td>
<td>5.0</td>
<td>4.8</td>
<td>4.0</td>
</tr>
<tr>
<td>CO (litre min⁻¹)*</td>
<td>5.0</td>
<td>4.7</td>
<td>6.0</td>
</tr>
<tr>
<td>VO₂ (ml min⁻¹)</td>
<td>250</td>
<td>226</td>
<td>9.6</td>
</tr>
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<table>
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<th>Hyperdynamic pattern</th>
<th>True value</th>
<th>Measured value</th>
<th>% Error</th>
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<td>98</td>
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<tr>
<td>SvO₂ (%)*</td>
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<td>85.9</td>
<td>1.0</td>
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<td>Haemoglobin concentration (g litre⁻¹)</td>
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<td>Arterio-venous difference (ml dl⁻¹)</td>
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<td>14.3</td>
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<tr>
<td>CO (litre min⁻¹)*</td>
<td>12</td>
<td>11.3</td>
<td>5.8</td>
</tr>
<tr>
<td>VO₂ (ml min⁻¹)</td>
<td>250</td>
<td>203</td>
<td>18.8</td>
</tr>
</tbody>
</table>

mimic CO and arterio-venous oxygen content data with large measurement errors.⁶¹ If these random data are used to calculate pairs of values that represent CO and VO₂ (the product of CO and arterio-venous oxygen content difference), they can be replotted as a CO vs VO₂ plot. Under these circumstances CO vs VO₂ plots tend to result in positive correlations with a correlation coefficient of 0.7; this is entirely a mathematical phenomenon.² If the original clinical measurements have large associated errors there is a tendency for the data to behave like random numbers and lead to artifactual positive correlations in DO₂/VO₂ plots. Mathematical coupling is also likely when interventions with a positive endpoint are made, such as increasing DO₂ with fluids or inotropes until a certain increase in CO has occurred. This therapeutic intervention is commonly undertaken in the ICU, but tends to select out positive measurement errors for CO. These positive errors are used in the inverse Fick calculation of VO₂, so that this value appears to increase at the same time.

These mathematical errors cause confusion in the ICU because the data suggest supply-dependency of VO₂ on DO₂. This was a confounding factor in many studies that either sought to demonstrate a pathological supply-dependency during critical illness, or used treatment that manipulated DO₂ to a particular value of VO₂. It is possible to reduce mathematical coupling error by applying a statistical correction, but this is impractical in the routine clinical setting.⁴²⁵³ Mathematical coupling error can be reduced by improving the accuracy of individual measurements by using the average of several values, and in particular by using separately measured CO values in the VO₂ and DO₂ calculations.¹⁹

It is widely accepted that if an accurate assessment of the relationship between DO₂ and VO₂ is required in the critically ill, VO₂ should be measured by direct gas analysis.¹⁵ This eliminates the possibility of mathematical coupling error.

Measurements based on gas analysis

Gas analysis techniques are not subject to many of the limitations of the inverse Fick method. In particular, continuous measurements are possible and the techniques are non-invasive. The indirect calorimetry techniques used in commercially available devices can broadly be classified as closed or open.

Closed circuit techniques

These can be considered modifications of closed water-sealed spirometry systems, which many consider the experimental gold standard for VO₂ determination. Carbon dioxide and water vapour are removed from re-circulating gas within a closed circuit. Oxygen is added to the system in order to maintain a constant content. The oxygen added corresponds to VO₂. For VO₂ measurement CO₂ concentration in the expired gas and an estimate of gas flow are used. Closed system methods have rarely been used for ventilated patients because of methodological limitations. In particular, it is difficult to use these devices with modern intensive care ventilators, which are based on open circuits. Any leaks in the system, changes in resistance and gas compression, and changes in end expiratory lung volume can introduce large measurement errors. These factors, together with the necessity for frequent changes in ventilator settings in the critically ill, make closed system techniques clinically impractical.
Open circuit techniques

Most widely used and validated devices for use in mechanically ventilated patients are based on open circuits. This method requires the accurate measurement of inspiratory and expiratory concentrations of oxygen and carbon dioxide. There are two possible methods of deriving $V_{\text{O}_2}$ and $V_{\text{CO}_2}$.

Measurement of both inspiratory and expiratory volume. If inspiratory volume ($V_I$) and expiratory volume ($V_E$) are measured, gas exchange can be calculated from the simple equations:

$$\dot{V}_{\text{O}_2} = (F_{\text{O}_2} \times V_I) - (F_{\text{E}_2} \times V_E)$$
$$\dot{V}_{\text{CO}_2} = (F_{\text{CO}_2} \times V_I) - (F_{\text{E}_2} \times V_E).$$

This approach is subject to large measurement error, because the accurate measurement of flow and gas volumes are difficult in ventilated patients (see below). Most modern devices have derived ways of measuring $V_{\text{O}_2}$ and $V_{\text{CO}_2}$ from only one ventilatory volume (inspiratory or expiratory). Some of the most accurate devices have used dilution methods to remove the need to measure tidal or minute volume altogether. All methods that do not directly measure inspiratory and expiratory volume are based on the Haldane transformation.

Haldane transformation. If no other gases are present other than oxygen, carbon dioxide, and nitrogen (assuming the ‘inert gases’ have insignificant and constant concentration) substitutions into physiological equations can be made to avoid the need to measure either $V_I$ or $V_E$. The important assumption is that nitrogen exchange is not occurring into or from the body. Exchange of any other gases, such as nitrous oxide, also invalidate this approach. The presence of a ‘steady state’ is a prerequisite for metabolic gas exchange measurements with modern devices. The Haldane transformation is summarized in Table 5.

Methodological issues in mechanically ventilated critically ill patients

The correct use and interpretation of gas exchange measurements in the ICU requires an appreciation of methodological issues and limitations associated with the techniques. Unless these are widely appreciated there is a danger that mistakes made in using the inverse Fick method may be repeated with modern gas analysis techniques.

Measurement in non-intubated patients. Gas exchange measurements during spontaneous breathing are usually made using canopy systems. Systems based on masks and mouthpieces are widely used in experimental settings, but require subject acclimatization to avoid erroneous hyperventilation. Canopy systems utilize high gas flows to avoid carbon dioxide accumulation (typically >40 litre min$^{-1}$). This results in gas dilution and the need to detect very small differences in gas concentrations. These systems are therefore prone to inaccuracy at high $F_{\text{O}_2}$, because differences become too small for reliable detection. These measurements are therefore impractical for most spontaneously breathing critically ill patients in the ICU. A detailed description of canopy-based systems for measurement of gas exchange is beyond the scope of this review, but can be found elsewhere.$^{12}$

Measurement in intubated patients. Routine on line measurement of gas exchange in intubated patients is possible as a result of recent technical advances. Several potential sources of error exist that require consideration to ensure that measurements are accurate and valid.

Oxygen and carbon dioxide measurement. The paramagnetic oxygen sensor is the standard means of measuring oxygen concentrations in modern devices; analysers based on infrared absorption are used for carbon dioxide measurement. Gases are generally sampled at fixed flow rates from the ventilator circuit and drawn into the device. Accurate gas exchange measurements require features that have largely been solved with modern devices.

Rapid-response time. This is needed for breath-by-breath analysis and to detect changes in gas concentration when breathing patterns are irregular. The response time requirement depends on the ventilatory frequency (RR). A simple guide relating the maximum ventilatory frequency for which the analyser is accurate to the 10–90% response time ($t_{10-90}$) is:

$$\text{RR}_{\text{max}} \,(\text{bpm}) = 10/t_{10-90} \,(s).$$

Most modern devices have a response time of about 0.15–0.2 s and are therefore accurate up to ventilatory frequencies of 40–50 bpm. This is an important consideration in tachypnoeic patients, for example during weaning. The validity of measurements decreases at high ventilatory frequencies, particularly for devices that rely on breath-by-breath analysis (e.g. M-COVX$^\text{T}$, Datex-Ohmeda, Helsinki) rather than mixing chambers (e.g. Deltatrac$^\text{T}$, Datex-Ohmeda, Helsinki).

Accuracy and linearity of measurements. Infrared carbon dioxide absorption measurements are non-linearly related to concentration so that corrections must be made to linearize the relationship. This must be done with high precision for gas exchange measurement; the systems used are therefore more complex than in simple capnometry. In addition, the systems rely on accurate and regular calibration. Failure to calibrate carefully in accordance with individual manufacturers guidelines can result in significant inaccuracy.

High gas pressures. A characteristic of mechanical ventilation is that pressure in the inspiratory limb of the breathing circuit fluctuates during the respiratory cycle. With modern ventilation techniques PEEP is applied to most patients in
the ICU. Levels of PEEP of 5–15 cm H2O may be applied even in the absence of severe lung injury. It is therefore necessary for gas concentration measurements in the inspiratory and expiratory limbs to be made by the same analyser under different pressure conditions. This is particularly problematic because high pressure can alter gas partial pressures. Modern devices compensate for these pressure fluctuations by measuring pressure in the sampling tubing and applying pre-determined compensation coefficients. Inaccurate pressure compensation can cause large measurement errors, particularly at high FiO2, because the absolute error becomes large compared with the FiO2 – FeO2 difference.

### System leaks

Most open system devices rely on collection of expired gas volume. Leaks from the patient-ventilator circuit can cause error. The exact nature of the systematic error introduced by a leak depends on the site at which it occurs and the device design. Common sources of leaks are around tracheal tubes, humidifiers, and from chest drains. These may be increased by high inspiratory pressures or PEEP. Any suction applied to the system simulates leak and invalidates measurements. Leaks make gas exchange measurement in children with uncuffed tracheal tubes extremely difficult, although some investigators have attempted this. A leak occurring from the mixing chamber of a Deltatrac™ has been described as a source of systematic error.

### High inspired oxygen concentration

Gas exchange measurements rely on the accurate measurement of gas concentrations to detect small differences between inspired and expired values. This is particularly true when the Haldane transformation is used because even small errors are magnified by the equation. This is analogous to the problem of error magnification with the inverse Fick method described above. For most mechanically ventilated patients FiO2 – FeO2 difference decreases as FiO2 is increased to treat hypoxaemia. Gas exchange measurement error increases disproportionately above an FiO2 of 0.6 and there are no automated devices that are reliable at FiO2 greater than 0.8. Most commercially available devices recognize this and include rejection algorithms for conditions where the FiO2 – FeO2 difference is too small for analysis. This is the major limitation of gas exchange measurements in the ICU, but it is worth noting that VCO2 measurement usually remains valid.

### Unstable inspired oxygen concentration

Fluctuation in FiO2 during the inspiratory cycle is a common feature of modern ventilators because of the design of oxygen blenders and the absence of a mixing chamber in most modern machines. It is most likely during spontaneous breathing modes because of breath-by-breath variation in gas delivery. This can result in unstable FiO2 – FeO2 difference and unstable VO2 measurements. These problems are exacerbated by high inspiratory pressures and at high FiO2, for the reasons discussed above. This problem can be difficult to solve in practice. It should be suspected if large minute-by-minute fluctuations in VO2 are observed in apparently stable patients. Individual ventilator manuals may include information concerning FiO2 stability. Newer systems that use breath-by-breath analysis (e.g. M-CO2X™) may be less subject to these inaccuracies. Various complex solutions have been suggested such as the addition of a mixing chamber or the use of additional pressure regulators. Most clinicians are unlikely to consider greater accuracy of VO2 measurement would justify ventilator modification. A simple measure that decreases fluctuation is to include an active humidifier chamber in the inspiratory limb, which improves gas mixing. Placing the monitor gas sampling line close to the patient also allows maximum mixing of inspiratory gas.

### Ambient temperature, pressure, and humidity

Gas volumes vary with temperature and ambient pressure. In addition, respiratory gases contain water vapour, which contributes a partial pressure. These factors must be accounted for in accurate gas exchange measurements. Adjusting gas volumes for temperature and ambient pressure is straightforward using the gas laws. Most modern devices adjust for temperature and ambient pressure, but regular calibration of ambient pressure may be required (e.g. Deltatrac™). Data are usually presented as standard or ambient temperature and pressure, dry gas (STPD and ATPD, respectively) or at body temperature (37°C) and pressure, gas saturated with water vapour (6.26 kPa) (BTPS). It is important to note the conditions expressed by monitors.

Most gas analysers measure partial pressure, which means the effect of water vapour can be important. This was a source of error in early devices, but is corrected for in modern automated systems. Two approaches have been used: first, sampled gas is dried before measurement or secondly, humidities of all gases measured are equalized with ambient air humidity using special tubing material, which is selectively permeable for water vapour (e.g.}

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**Table 5** Derivation of the Haldane transformation, the principle used in most metabolic monitors

\[ V_{O2} = (V_i \times F_{iO2}) - (V_e \times F_{eO2}) \]  
(1)

Assuming nitrogen is at steady state (no net loss or gain from the body):

\[ V_i \times P_{N2} = V_e \times P_{N2} \]  
Therefore:

\[ V_i = V_e (F_{iN2} / F_{eN2}) \]  
(2)

From (1) and (2):

\[ V_{O2} = V_e [(F_{iO2} \times F_{iN2}) - (F_{eO2} \times F_{eN2})] \]  
(3)

If inspired gas contains no gases other than O2 and N2:

\[ P_{iO2} = 1 - F_{iN2} \]  
(4)

And

\[ F_{eN2} = 1 - F_{eO2} \]  
(5)

Combining (3), (4), and (5) gives:

\[ V_{O2} = V_e \times ([F_{iO2} \times (1 - F_{iN2}) - F_{eN2}]) \times (1 - F_{eN2}) \]  
(6)
Flow measurements. Devices that measure flow usually derive \( V_O_2 \) and \( V_CO_2 \) using the Haldane transformation from either inspiratory or expiratory volume. Highly accurate flow sensors are available that perform well under ideal conditions, namely static flow of clean dry gas. Pneumotachographs are most commonly used for this purpose. Problems arise when human respiratory flow is measured under clinical conditions. In the ICU excessive secretions, high humidity, and variable flow patterns are common in the ventilator circuit. Any interruption to flow can alter the characteristics of the flow meter, resulting in systematic errors in gas exchange measurements. Filters and Heat and Moisture Exchangers placed at an appropriate position in the inspiratory circuit can decrease these, but it is important to check that the characteristics of the sensor are not altered. Regular checks for moisture and secretions are necessary, particularly during prolonged measurement.

Ventilators that use continuous flow pneumatic techniques can make gas exchange measurements impractical. High flow rates in the circuit dilute gas concentrations to very low levels, which result in unacceptable measurement error. Systems in which continuous flow cannot be turned off may make metabolic measurements using gas exchange devices impossible.

Lack of steady state. For accurate \( V_O_2 \) and energy expenditure determination the patient must be in a steady state for inert gases, most importantly nitrogen. The presence of small concentrations of non-inert gases, such as volatile anaesthetics and nitric oxide, will reduce the accuracy of measurements. At therapeutic gas concentrations the inaccuracy is small and in most cases is not clinically significant. Devices that compensate for volatile anaesthetic use, which are intended for use during anaesthesia, are now available. In addition, sudden changes in carbon dioxide steady state decrease the validity of \( V_O_2 \) and energy expenditure determination until steady state is fully re-established. After changes in ventilation complete steady state is not fully re-established for 30–60 min, but as the majority of change occurs in the initial minutes clinically important inaccuracy usually only lasts for 5–10 min. Continuous gas exchange monitoring allows tracking of changes and visual confirmation of new steady state. Even after complex physiological disruptions, such as after liver reperfusion during transplantation, steady state usually appears to be re-established within 10 min.59

Current gold standard for gas exchange measurements

Many systems for measurement of gas exchange in mechanically ventilated patients have been used in the ICU. The performance of these devices is highly variable, because of the many problems discussed above. The most widely used system is Deltatrac™. This has undergone a number of independent laboratory and clinical validations and evaluations and is usually considered the gold standard for gas exchange measurement in the critically ill.

Principles of measurements

During mechanical ventilation inspired gas is sampled from the inspiratory circuit and all expired gas is collected via tubing from the common gas outlet of the ventilator and passed into a mixing chamber. The RQ is calculated from inspiratory and expiratory gas fractions alone, using a formula derived using the Haldane transformation, from measurements made from the inspiratory limb of the circuit and from the mixing chamber:

\[
RQ = 1 - \frac{F_{I_O_2}}{F_{E_O_2} - F_{E_CO_2} - F_{I_O_2}}
\]

Gas from the mixing chamber is drawn through a highly accurate fixed flow generator. \( V_CO_2 \) is calculated as the product of the constant flow and the concentration of carbon dioxide downstream from the mixing chamber. The \( V_O_2 \) is subsequently calculated from RQ and \( V_CO_2 \) from the equation:

\[
V_O_2 = V_CO_2 / RQ.
\]

The system therefore removes completely the need to measure accurate gas volumes, but relies on the accuracy of the gas fraction measurements and the flow generator. Water vapour in respiratory gases or dry calibration gases is balanced with ambient air using a water trap and Nafion tubing (see above). With this system the humidity of analysed gases is equalized with ambient air before measurements. Thereafter, gas fractions are expressed at STP.

Regular and careful calibration is required. During use the machine performs baseline checks for carbon dioxide and oxygen every 10 min. Correction for inspired carbon dioxide fraction is made by assuming that the carbon dioxide fraction of the oxygen/air mixture decreases linearly from 0.04 to 0% as \( F_{I_O_2} \) changes from 21 to 100%. Before each use the machine is calibrated against a standard gas mixture and ambient barometric pressure. Modern versions (Deltatrac III™) perform these automatically. Approximately every 3–6 months the accuracy of the flow generator should be checked using an alcohol burn. A qualitative alcohol burn checks the overall accuracy of the machine and is quick and simple; the RQ measured by the machine should be 0.67. A quantitative burn of an accurately measured volume of pure alcohol, which will produce a predictable volume of carbon dioxide, can be used to make fine adjustment to the flow generator. The drift in flow
generator calibration has been shown to be negligible over 3 months. Gas injection techniques using carbon dioxide and/or nitrogen can also be used to simulate $V_{CO2}$ and $V_{O2}$ in order to calibrate the flow generator.

**Accuracy**

A number of studies have assessed the accuracy of the machine in laboratory studies and under clinical conditions. Most of these authors found negligible inaccuracy in association with increasing levels of PEEP up to about 20 cmH2O. The effect of increasing $F_{I,O2}$ was also small and relative errors of less than 5% occurred even at $F_{I,O2}$ 0.8.37 Using lung model simulations of increases in oxygen consumption, Ronco and Phang found the Deltatrac™ could detect changes with an error of less than 1%.47 The most detailed clinical validation in ventilated patients was carried out by Tissot and colleagues who compared $V_{O2}$ and $V_{CO2}$ by the Deltatrac™ with measurements made using a mass spectrometer and with the Douglas bag method in ventilated critically ill patients. The Deltatrac™ gave values that agreed closely with measurements with both methods and any disparity was clinically insignificant.56

Deltatrac™ solves many of the problems associated with gas exchange measurements in the ICU. Disadvantages are a high cost, large size, and the need for rigorous calibration procedures. Recent developments represent a trade-off between miniaturization and integration of measurement devices with routine monitoring systems, and loss of precision in comparison with Deltatrac™.

**New devices**

The most recently marketed device, the M-COVX™ (Datex-Ohmeda, Helsinki, Finland), is a bedside module that integrates with ICU monitoring systems. The main advantages over Deltatrac™ are compact size, system integration, and lower cost. The principle of measurement is different: a flow sensor located at the patient airway measures tidal volume based on the pressure decrease across a turbulent flow restrictor,33 and gas fractions are determined by a standard side stream analyser. The technical advance in the system is integrating the flow signal, which is instantaneous, with the gas fraction measurement, which has a 1–2 s delay. Complex software reconstructs the two signals and integrates them using the Haldane transformation. The system has a quoted accuracy of ±10% up to an $F_{I,O2}$ of about 0.7 and a ventilatory frequency of <35/min. Comparison with Deltatrac™ suggests that acceptable agreement occurs, particularly at $F_{I,O2}$ values less than 0.5.32 The response time for detecting changes in metabolic gas exchange may be shorter with this system because it calculates breath-by-breath values rather than relying on changes in a mixing chamber. For clinical measurements in ICU patients the major source of error appears to be inaccuracy of tidal volume measurements caused by water condensation in the flow sensor.46

**Potential applications of gas exchange measurements in the ICU**

The utility of gas exchange measurements in the ICU is uncertain. For oxygen kinetics, much of this uncertainty results from the confusion regarding measurement techniques and their limitations. For nutritional assessment, the more frequent use of protocol guided enteral nutrition has decreased interest in accurate metabolic assessment in most ICUs. Until recently, the high cost of accurate metabolic monitors has also discouraged metabolic gas exchange assessment as part of standard therapy.

There are no large clinical trials in ICU patients that test the impact of modern metabolic gas exchange measurement on clinically important outcomes such as mortality, ventilation time, nutritional status or ICU length of stay. The current technology has several potential applications for clinical management.

**Nutritional assessment**

Energy expenditure measurements can be used to guide the dose of either enteral or parenteral nutrition. It is uncertain what level of under- or over-nutrition in relation to measured energy expenditure has clinically important adverse effects during critical illness. Over nutrition can cause hyperglycaemia, which may have adverse effects during critical illness and excessive lipogenesis can cause liver injury. Predictions made using equations for energy requirements have poor agreement with measured values made using metabolic monitors in the ICU.14 Feeding can also increase $V_{CO2}$ either because of high carbohydrate intake (RQ=1) or excessive calorie intake.3 Gas exchange measurements may be useful in the ‘difficult to wean’ patient in order to optimize nutrition when ventilatory failure is the principal clinical problem. New compact systems for measuring energy expenditure in the ICU make this a feasible routine monitor, but more work is needed to establish whether these measurements translate into clinical benefit.

**Measuring metabolic stress**

Inflammation is associated with increased $V_{O2}$ and energy expenditure. For example, patients with sepsis syndrome have higher energy expenditure than patients with systemic inflammatory response syndrome (SIRS) alone or those without SIRS.35 Energy expenditure measurements may be particularly useful in managing conditions associated with large increases in energy expenditure, such as major burns. Higher $V_{O2}$ has also been positively correlated with higher circulating concentrations of pro-inflammatory cytokines after cardiopulmonary bypass.59 Energy expenditure meas-
Measurements are also useful in complex metabolic disorders such as fulminant hepatic failure in which metabolic rate is clinically difficult to assess. Measuring VO₂ in ICU patients may assist clinical management by providing an indirect measure of metabolic stress. Changes in VO₂ in response to interventions such ascooling or anti-inflammatory agents may be a useful measure of efficacy. Conversely, routine monitoring can detect acute increases in metabolic demand that could cause patient distress or myocardial ischaemia. These typically occur during physiotherapy or during weaning trials (Fig. 2).

**Oxygen kinetics**
A low VO₂ is associated with adverse outcome in many forms of critical illness, especially in sepsis. In addition, the inability to increase VO₂ in response to fluids and inotropic agents that increase DO₂ is a strong predictor of high mortality. These studies used inverse Fick calculations, which are now performed infrequently in many ICUs because of concerns about the utility of PA catheters, adverse effects associated with their use, and the validity of VO₂ calculations. Recent studies, and meta-analyses of previous trials of therapy with CO, DO₂ or VO₂ as therapeutic goals, suggest that optimizing DO₂ or VO₂ may improve clinical outcomes if the interventions are performed early and/or before organ failure has become established. Non-invasive gas exchange measurement is a potential goal of resuscitation in ventilated patients, but has not been assessed in clinical trials.

**Assessment of pulmonary physiology**
The accurate measurement of carbon dioxide concentration, VO₂, minute volume and Paco₂ make an accurate assessment of alveolar ventilation and respiratory deadspace feasible in mechanically ventilated ICU patients. These values have not been integrated into commercially available systems, but are potential future applications of the technology. Changes after ventilator adjustments may be useful in the management of acute lung injury or during difficult weaning. Further work is required in this area.

Several studies have used the difference between inverse Fick and gas analysis methods of VO₂ determination to estimate pulmonary VO₂. This physiological variable is of interest in pulmonary inflammatory conditions, such as acute lung injury and pneumonia, because it may be substantially increased and associated with injury severity. The validity and clinical accuracy of this calculation are uncertain because it needs many measurements to obtain the value, each with associated errors.

**Conclusions**
Major advances have been made in our ability to measure metabolic gas exchange in ventilated patients. Part of this progress has been a greater understanding of the limitations of these challenging measurements. Currently available approaches can provide an accurate and reproducible method of measuring VO₂, VO₂ and related variables in most critically ill patients. Much of the existing literature is confusing and contradictory, in part because important methodological issues have not been widely appreciated until recently. Further work using new technology is needed before the clinical value of metabolic gas exchange measurement in the ICU is fully understood.

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