Handbook of Gas Exchange and Indirect Calorimetry
HANDBOOK OF GAS EXCHANGE
AND INDIRECT CALORIMETRY

by

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LIST OF SYMBOLS AND ABBREVIATIONS

A  age in years
ATPD  atmospheric temperature and pressure, dry gas
BEE  basal energy expenditure
BTPS  body temperature and pressure, saturated gas
C\text{ao2}  oxygen content of arterial blood (ml/L)
C\text{vo2}  oxygen content of venous blood (ml/L)
CHO  carbohydrate oxidation rate (g/day)
CO  cardiac output (L/min)
DO\text{2}  oxygen delivery (ml/min)
EE  energy expenditure (kcal/24h)
F  fat oxidation rate (g/day)
F\text{aco2}  alveolar CO\text{2} concentration
F\text{ddo2}  inspiratory-mixed expiratory O\text{2} difference
F\text{eo2}  mixed expired O\text{2} concentration
F\text{dco2}  diluted CO\text{2} concentration
F\text{eko2}  mixed expired CO\text{2} concentration
F\text{en2}  mixed expired N\text{2} concentration
F\text{i02}  inspired O\text{2} concentration
F\text{ico2}  inspired CO\text{2} concentration
F\text{in2}  inspired N\text{2} concentration
H  height (cm)
Hb  hemoglobin content concentration of blood (g/L)
k\text{1}  volume of oxygen bound by 1 g of hemoglobin (ml/g)
k\text{2}  conversion constant, k\text{2} = 8.16
npRQ  non-protein RQ
np\text{vo2}  non-protein oxygen consumption
np\text{pc02}  non-protein carbon dioxide production
p  pressure
p\text{ao2}  arterial O\text{2} partial pressure (kPa, mmHg)
p\text{aco2}  arterial CO\text{2} partial pressure (kPa, mmHg)
p\text{vo2}  venous O\text{2} partial pressure
PEEP  positive end-expiratory pressure
Q  flow (L/min)
R  molar gas constant
REE  resting energy expenditure
RQ  respiratory quotient
S\text{ao2}  hemoglobin saturation of arterial blood
S\text{vo2}  hemoglobin saturation of venous blood
STPD  standard temperature and pressure (0°C, 760 mmHg), dry gas
T  temperature (K)
t  time (min)
U\text{N}  urinary nitrogen excretion (g/day)
V  volume (L)
\dot{V}\text{a}  alveolar ventilation (L/min)
\dot{V}\text{d}  dead space (ml)
\dot{V}\text{e}  expired minute volume (L/min)
\dot{V}\text{i}  inspired minute volume (L/min)
\dot{V}\text{t}  tidal volume (ml)
\dot{V}\text{o2}  oxygen consumption (ml/min)
\dot{V}\text{co2}  carbon dioxide production (ml/min)
W  weight (kg)
\dot{w}\text{N2}  nitrogen infusion rate (ml/min)
\dot{w}\text{co2}  carbon dioxide infusion rate (ml/min)
The purpose of this book is to give the necessary physiological, clinical and technical background to understand gas exchange measurements. Recent technological breakthroughs have made compact gas exchange monitors or metabolic monitors commercially available, but this does not change the fact that a thorough understanding of all the complex phenomena involved in these measurements will considerably help in obtaining clinically meaningful and useful results.

In the clinical section of this book a special emphasis has been put on the measurement of gas exchange in the critically ill patients with severe respiratory and hemodynamic problems.

In the technical sections much of text has been devoted to the basic question of accuracy, simulation methods to check the overall performance of the measurement system. These methods are also routinely used in the quality control of the devices, which should mean a diminishing need to perform the checks in the clinics.

The authors hope that this book together with its list of references, is able to increase understanding of the respiratory gas exchange measurements and give help in problems arising in several application fields.
INTRODUCTION

Interest in the measurement of respiratory gas exchange has increased tremendously during the last decade. Clinicians and scientists in various fields of medicine have seen the potential of accurate measurement of carbon dioxide production ($\dot{V}_{\text{CO}_2}$) and oxygen consumption ($\dot{V}_{\text{O}_2}$) as a valuable tool for diagnostic and therapeutic purposes. Clinical applications vary from assessment of energy requirements and response to nutrition in malnutrition and obesity to comprehensive analysis of ventilation and oxygen transport in intensive care patients with complex respiratory and hemodynamic problems.

The basics of energy metabolism were established by Lavoisier, Priestley, and Black 200 years ago. They demonstrated that combustion was an oxygen consuming, heat producing process, and that energy metabolism consumed oxygen and produced heat. These observations stimulated research on the interactions of food, physical activity and temperature with heat production. Various calorimetric techniques were developed for these purposes, and by the beginning of this century, the energy content of foods had been determined and energy requirements in populations had been studied. Early in the 20th century, Benedict and Atwater demonstrated that heat production in humans could be determined indirectly by measuring respiratory gas exchange and computing the corresponding heat production from the energy content of nutrients. These measurements correlated closely with the results obtained by direct calorimetry. Indirect calorimetry was thus established as an accepted method for measurement of energy expenditure and substrate utilization in humans /1-3/.

Following the pioneering clinical work by Benedict, Atwater, Lusk and DuBois, energy expenditure measurements became clinical routine /1-5/. Basal metabolic rate was the standard test for the diagnosis and follow-up of thyroid function. The use of indirect calorimetry in thyroid diseases was subsequently replaced by more specific tests, and simultaneously, interest in energy expenditure in other conditions also diminished.

Several factors have prompted the recent interest in gas exchange measurements. Since the classic studies by Cuthbertson in the early 1930's, accidental and surgical trauma and infection have been known to increase energy expenditure /6-8/. The association of increased energy expenditure with postinjury weight loss and morbidity was brought into focus by Kinney in the late 1960's and early 1970's /9-11/. The use of total parenteral nutrition (TPN) for the treatment and prevention of injury- and infection-related weight loss and nutritional deterioration became popular and the need for practical, easily applicable methods for the measurement of energy expenditure
became clear /11-13/. The development of modern intensive care and advanced life support systems, especially mechanical ventilation, have stimulated interest in the measurement of gas exchange for the analysis of ventilation and oxygen transport in the critically ill patients. The possibility of disorders in oxygen utilization in the adult respiratory distress syndrome (ARDS) and septic shock has gained wide support /14-16/ and much research has focused on the oxygen transport system in these states /14-18/. The potential benefits from gas exchange measurements in the intensive care environment have certainly been known from the beginning of the era of mechanical ventilation.

The main reason that these measurements have not been part of the intensive care routine, has been the lack of suitable equipment. While accurate measurements of gas exchange in the healthy, spontaneously breathing subject has been a task that requires devotion and attention to details, the positive airway pressures, high inspiratory oxygen concentrations, humidity, and secretions in the mechanically ventilated patient have, until recently, presented unsurmountable problems for instrument design.

Commercial instruments for the measurement of gas exchange in the intensive care setting have now been available for several years. Interestingly, most, if not all, have been developed and marketed for measurement of energy expenditure, “calorimetry”. Their development was, at least in part, inspired by studies indicating that not only undernutrition but also overfeeding could be harmful to the patient, especially by increasing the ventilatory demand /19-22/. The wide variation of the measured to predicted ratio of energy expenditure in the acutely ill patient has also underscored the need to measure the actual energy expenditure, at least in patients with prolonged nutritional problems /23-25/. The modern equipment for indirect calorimetry will certainly increase our understanding of the nutritional requirements and response to nutrition in various disease states and help the clinician to provide optimum nutritional therapy. The possibility to measure gas exchange in the critically ill patient with life-threatening respiratory and hemodynamic problems opens up a new insight to the pathophysiology and management of several key areas of intensive care.

The technology for accurate gas exchange measurements in the critically ill patients is available, and the measurements can be performed relatively easily. However, accuracy and reproducibility of results can be obtained only if the investigator understands the basic principles of the measurement and related physiology, and pays meticulous attention to the details.
2 OXYGEN CONSUMPTION

Indirect calorimetry measures oxygen consumption as the amount of oxygen taken up from the respiratory gases. The prerequisite for tissue oxygen consumption is the transport of oxygen in the arterial blood to the regional capillary beds and the extraction of oxygen from the blood by the tissues. When oxygen delivery \( D_{O_2} = \text{cardiac output} \cdot \text{arterial oxygen content}, \) \( C_{aO_2} \) is adequate, \( v_{O_2} \) is independent from \( D_{O_2} \), whereas during inadequate \( D_{O_2} \), \( v_{O_2} \) depends on \( D_{O_2} \). Consideration of the factors contributing to the balance between oxygen supply and demand makes the interpretation and comprehensive utilization of gas exchange data easier.

2.1 Oxygen supply and demand

A model for both whole body and regional oxygen consumption can be described in terms of the oxygen contents of arterial and venous blood, and the blood flow draining the vascular bed:

\[
v_{O_2} = \text{blood flow} \cdot (C_{aO_2} - C_{vO_2}) \tag{1}
\]

For the whole body, the equation can be written as

\[
v_{O_2} = CO \cdot (C_{aO_2} - C_{vO_2}) \tag{2}
\]

where \( CO = \text{cardiac output}, C_{aO_2} = \text{arterial oxygen content}, \) and \( C_{vO_2} = \text{mixed venous oxygen content}. \) Blood oxygen content depends on the hemoglobin concentration and the partial pressure of oxygen. Accordingly, the equation describing the interrelation of \( v_{O_2} \) and whole body oxygen transport can be written as

\[
v_{O_2} = CO \cdot [(k_1 \cdot S_{aO_2} \cdot \text{Hb} + 0.031 \cdot p_{aO_2}) - (k_1 \cdot S_{vO_2} \cdot \text{Hb} + 0.031 \cdot p_{vO_2})] \tag{3}
\]

where \( k_1 \) is the volume of oxygen in ml bound by 1 gram of normal hemoglobin when fully saturated (estimated as 1.36 - 1.39 ml/g), \( S_{aO_2} \) and \( S_{vO_2} \) are the hemoglobin saturations of arterial and mixed venous blood, \( \text{Hb} \) is the hemoglobin concentration in grams per liter, \( p_{aO_2} \) and \( p_{vO_2} \) are the partial pressures of oxygen in arterial and mixed venous blood in
mmHg, and 0.031 is the solubility coefficient of oxygen in plasma. If oxygen partial pressures are expressed in kilopascals (kPa), the coefficient is 0.233.

According to Equation (2), any change in $v_{O_2}$ will be primarily reflected in $C_{vO_2}$, if CO remains constant. On the other hand, changes in CO may compensate for any change in $v_{O_2}$. Under normal conditions most of the blood entering the systemic circulation from the lungs will be saturated with oxygen, and therefore $v_{O_2}$ has little effect on the $C_{aO_2}$. However, when the venous admixture (or physiological shunt) increases, the changes in $C_{vO_2}$ induced by $v_{O_2}$ will be reflected more in the $C_{aO_2}$. In the presence of large shunt, high $v_{O_2}$ may contribute to arterial hypoxemia.

![Figure 1](image)

**Figure 1** The interrelation of $v_{O_2}$ and whole body oxygen transport

A patient with a $v_{O_2}$ of 300 ml/min, cardiac output of 10 L/min, blood hemoglobin 108 g/L and pulmonary shunt of .20 is shown. Increased $v_{O_2}$ is primarily reflected in decreased $S_{vO_2}$, although $S_{aO_2}$ decreases slightly as well (1). Increased shunt decreases both $S_{aO_2}$ and $S_{vO_2}$ to the same degree (2). Decreased
cardiac output reduces both $S_{ao2}$ and $S_{vo2}$, although the effect on $S_{vo2}$ predominates (3). Under these conditions, the low $S_{vo2}$ may limit the $v_{o2}$. Increased oxygen carrying capacity of the blood (increased hemoglobin) makes the same $v_{o2}$ possible at a narrower difference between $S_{ao2}$ and $S_{vo2}$ (4).

When $DO_2$ approaches the critical level, small changes in any of the variables in Equation (3) may become limiting for $v_{o2}$. Then tissue oxygen demand exceeds the $v_{o2}$ and anaerobic metabolism will ensue.

Acute changes in respiration, hemodynamics, and activity may induce wide variations in the $v_{o2}$ measured by any method. Indirect calorimetry provides convenient means for repeated long-term measurement of $v_{o2}$. The prolonged measurement period reduces the error induced by the acute variation and more valid information of the average gas exchange will be obtained. In practice, the duration of a single measurement should be at least 20 - 30 min.

2.2 Determinants of oxygen consumption

Under aerobic conditions, $v_{o2}$ depends on the metabolic activity of the tissues. The substrates of the energy metabolism also influence the $v_{o2}$ at a given metabolic rate, since different quantities of oxygen are required for the production of the same amount of energy from carbohydrate, fat, or protein. The amount of $v_{o2}$ required for one kcal of energy from carbohydrate is 207 ml, from fat 213 ml, and from protein 223 ml. Therefore, $v_{o2}$ varies at the same level of energy expenditure (EE) according to the mixture of substrates utilized /1, 26, 27/.

Various physiological and pathophysiological conditions have acute and long-term effects on $v_{o2}$. Any kind of stress, especially major surgical or accidental trauma, infection, fever, pain, physical activity and exercise, anxiety, hyperthyroidism, and nutrient intake increase $v_{o2}$/6-11, 28/. Factors that decrease $v_{o2}$ include starvation, severe hypothermia, and hypothyroidism /6-11, 28/. The magnitude of increase in $v_{o2}$ in acutely ill patients ranges from 0 - 20 % after elective surgery, 10-30 % after major accidental injury, up to 60 % in severe infections and sepsis, and up to 100 % in patients with large burns /6-11/. The wide, short-term, variation in EE that occurs in the clinical environment of an intensive care unit has clearly been demonstrated: the routine daily activities and the level of awareness of the patient caused up to 40 % variation in the $v_{o2}$/25-29/. These factors should be taken into account when clinical measurements of $v_{o2}$ are performed.
Figure 2 Determinants of $v_{O_2}$ and $v_{CO_2}$, epileptic convulsions

Any kind of acute or prolonged stress can affect $v_{O_2}$ and $v_{CO_2}$. Figure 2 shows continuous measurement of gas exchange in a patient with multiple injury, including cerebral contusion. The metabolic rate is increased, as indicated by the basal $v_{O_2}$ of approximately 300 ml/min. The major sporadic spikes of $v_{O_2}$ and $v_{CO_2}$ are caused by epileptic convulsions.

2.3 Anaerobic metabolism and oxygen debt

Oxygen consumption is determined by the metabolic rate and the substrates utilized by the tissues, providing that sufficient amount of oxygen is available. When oxygen delivery ($D_{O_2}$) is adequate, $v_{O_2}$ is independent of $D_{O_2}$. The adequacy of oxygen supply depends on the metabolic needs of the tissues, the efficiency of oxygen extraction, the cellular utilization of oxygen, and the distribution of blood flow to regional vascular
beds. When systemic or regional oxygen delivery is inadequate, \( \dot{v}_o \) becomes linearly dependent on \( D_{o2} \) and anaerobic metabolism with lactic acid production will ensue. Anaerobic metabolism may be due to:

1. reduced \( D_{o2} \) (e.g. hypovolemic or cardiogenic shock, arterial hypoxemia, anemia)
2. increased metabolic demands (e.g. convulsions, shivering, exercise)
3. maldistribution of blood flow (presumably in septic shock)
4. blocked cellular oxygen utilization (e.g. uncoupled oxidative phosphorylation in cyanide poisoning)

During anaerobic metabolism, \( \dot{v}_o \) does not reflect the metabolic activity of tissues. The anaerobic metabolism causes an oxygen debt. When aerobic conditions are re instituted, the oxygen debt is reflected as increased \( \dot{v}_o \). The development and magnitude of oxygen debt is clearly demonstrated, when \( \dot{v}_o \) is measured at rest, during strenuous exercise, and during the recovery from the exercise. The oxygen debt is the total amount of oxygen consumed that exceeds the resting \( \dot{v}_o \) after exercise has been stopped.

The oxygen debt will also be reflected in the respiratory quotient (RQ). During anaerobic conditions, the RQ will be higher than in corresponding aerobic conditions. When aerobic conditions are re instituted, the RQ will be low, until the oxygen debt has been paid.
3 CARBON DIOXIDE PRODUCTION

Indirect calorimetry is the only practical method to measure carbon dioxide production ($\dot{V}_{CO_2}$). Although $\dot{V}_{O_2}$ can be measured alternatively as the product of cardiac output and arteriovenous oxygen content difference, this is not feasible for $\dot{V}_{CO_2}$. Measurement of $\dot{V}_{CO_2}$ from the respiratory gases is vulnerable to errors unless the close interrelation of $\dot{V}_{CO_2}$, alveolar ventilation ($\dot{V}_A$), and arterial CO$_2$ is taken into account.

3.1 Carbon dioxide production and alveolar ventilation

The model for CO$_2$ removal from the body describes $\dot{V}_{CO_2}$ as a function of $\dot{V}_A$ and alveolar CO$_2$ concentration ($F_{ACO_2}$):

$$\dot{V}_{CO_2} = \dot{V}_A \cdot F_{ACO_2}$$  \hspace{1cm} (4)

The alveolar CO$_2$ concentration can be estimated to be equal to the arterial CO$_2$ concentration and the equation written as:

$$\dot{V}_{CO_2} = k_2 \cdot \dot{V}_A \cdot P_{aCO_2}$$  \hspace{1cm} (5)

where $k_2$ is a constant that converts arterial CO$_2$ partial pressure ($P_{aCO_2}$) to CO$_2$ concentration and the $\dot{V}_{CO_2}$ to standard pressure (760 mmHg) dry gas. When $\dot{V}_A$ is given in L/min, body temperature (37°C) and fully saturated with water vapour, and $P_{aCO_2}$ in kPa, $k_2 = 8.16$.

The minute ventilation ($\dot{V}_E$) required to produce a given $\dot{V}_A$, depends on the ratio of dead space to tidal volume ($V_D/V_T$):

$$\dot{V}_A = \dot{V}_E \cdot (1 - V_D/V_T)$$  \hspace{1cm} (6)

When Equations (5) and (6) are combined,

$$\dot{V}_{CO_2} = \dot{V}_E \cdot (1 - V_D/V_T) \cdot P_{aCO_2} \cdot k_2$$  \hspace{1cm} (7)

This equation demonstrates that the measurement of $\dot{V}_{CO_2}$ is sensitive to changes in ventilation; any change in $\dot{V}_E$ will directly affect $\dot{V}_{CO_2}$ until a new steady state has been achieved. Analogously, changes in breathing pattern will influence $\dot{V}_{CO_2}$. 

8
since changes in tidal volume will alter the $V_D/V_T$-ratio, even if $v_E$ remains unchanged. If the metabolic production of CO$_2$ remains constant, changes in $v_E$ and $V_D/V_T$ will change $P_{aCO_2}$ until a new steady state is obtained and the amount of CO$_2$ removed by ventilation corresponds to the metabolic production of CO$_2$.

3.2 Determinants of carbon dioxide production

In steady state, $v_{CO_2}$ depends on the metabolic activity of the tissues and the substrate of the energy metabolism. Production of 1 kcal of energy from fat produces 151 ml of CO$_2$, from protein 181 ml of CO$_2$, and from carbohydrate 207 ml of CO$_2$ (/1, 26, 27/). Therefore $v_{CO_2}$ varies at the same rate of EE depending on the mixture of substrates utilized in the energy metabolism. Since $v_{CO_2}$ is related to metabolic rate, the same factors that influence $v_{O_2}$ also affect $v_{CO_2}$. The change in $v_{CO_2}$ is not necessarily equal to the change in $v_{O_2}$. For example, when metabolic rate is increased by injury or sepsis, fat metabolism tends to increase and the RQ decreases. Accordingly, the increase in $v_{CO_2}$ is smaller than the increase in $v_{O_2}$.

If any of the variables in Equation (7) changes, the body pool of CO$_2$ will change. If the measured $v_{CO_2}$ should reflect the metabolic production of CO$_2$, enough time should be allowed for the body pool of CO$_2$ to equilibrate in the new steady state. The time required for the CO$_2$ pool to equilibrate, after a major change in the metabolic $v_{CO_2}$ or ventilation, may vary from 30 to 120 min or take even longer /30-31/. In practice, a period of 60 min after a change is often sufficient. Continuous measurement of gas exchange allows evaluation of the steady state. In mechanically ventilated patients, a stable end-tidal CO$_2$ concentration, if this variable is available, is a further indicator of equilibrated CO$_2$ pool.
An abrupt change in minute ventilation (arrow) from 10 L/min to 11 L/min with a constant frequency of 12/min during controlled mechanical ventilation causes an immediate increase in the measured $\dot{v}_{\text{CO}_2}$, which gradually decreases towards the initial $\dot{v}_{\text{CO}_2}$ when a new steady state in the body pool of CO$_2$ is approached. The metabolic $\dot{v}_{\text{CO}_2}$ is constant, and the change in the measured $\dot{v}_{\text{CO}_2}$ entirely reflects the change in the body pool of CO$_2$ caused by the increased alveolar ventilation.
A rapid increase in the peripheral circulation during the rewarming phase after open-heart surgery increases $v_{\text{O}_2}$ and $v_{\text{CO}_2}$. Since alveolar ventilation is adjusted to match the increased $v_{\text{CO}_2}$, a new steady state in gas exchange is achieved more rapidly than without the adjustment. A prolonged sampling period and blood gas analysis or end-tidal CO$_2$-monitoring is required under these conditions in order to avoid misinterpretation of $v_{\text{CO}_2}$ due to the major changes in the body pool of CO$_2$. 

Figure 4  Determinants of $v_{\text{O}_2}$ and $v_{\text{CO}_2}$ increasing peripheral circulation
Protein oxidation should be measured, if EE is to be estimated as precisely as possible by indirect calorimetry.

Protein is not completely oxidized in the body. The contribution of protein oxidation to the total $v_{O_2}$ and $v_{CO_2}$ can be estimated by measurement of the urinary excretion of nitrogen. One gram of urinary nitrogen corresponds to 6.25 grams of oxidized protein /26-27/. The values used for $v_{O_2}$ and $v_{CO_2}$ corresponding to one gram of urinary nitrogen vary from 5.94 L to 6.03 L of $O_2$ per gram urinary nitrogen and from 4.76 L to 4.88 L of $CO_2$ per gram urinary nitrogen /26-27/. The actual values depend on the composition of the protein. Nevertheless, these factors can be used to assess the $v_{O_2}$ and $v_{CO_2}$ caused by protein oxidation. If this is subtracted from the total $v_{O_2}$ and $v_{CO_2}$, the remaining $v_{O_2}$ and $v_{CO_2}$ is entirely due to the oxidation of fat and carbohydrate.

Measurement of urinary excretion of nitrogen is often impractical in the clinical circumstances. Also, the nitrogen excreted to the urine is not oxidized at the time it is excreted to the urine, whereas the measured gas exchange reflects on going metabolic activity without comparable time-lag. For most purposes, gas exchange data alone gives sufficient information of the energy expenditure, even if the urinary excretion of nitrogen is only estimated or its effect taken into account in the formulas used to calculate EE from gas exchange data. Since the RQ of protein is 0.8, between the RQ of fat (0.7) and carbohydrate (1.0), and the urinary excretion of nitrogen due to protein oxidation varies within relatively narrow limits (usually between 5 and 25 g/day and practically never above 40 g/day), only a small error is made if EE is estimated from respiratory gases alone /26, 27, 31, 32/. Various formulas have been developed for this purpose, and the error analysis of the estimated EE indicates that in practically all clinical circumstances the error in the estimated EE is less than 5 % /26, 27, 31, 32/.

Most applications of indirect calorimetry do not require measurement of urinary nitrogen excretion. Even if EE is the main focus of the measurement, only small errors are induced, if urinary nitrogen is not measured.
5  RESPIRATORY QUOTIENT

5.1  Definition

The ratio between CO\textsubscript{2} production (v\textsubscript{CO\textsubscript{2}}) and O\textsubscript{2} consumption (v\textsubscript{O\textsubscript{2}}) associated with metabolic processes at cellular level is called the **respiratory quotient**.

\[
RQ = \frac{v_{CO_2}}{v_{O2}}
\]  

(8)

The results obtained from gas exchange measurements are identical with actual metabolic quantities only when the CO\textsubscript{2} and O\textsubscript{2} pools of the body are in steady state (see Figure 5). In a general case, the precise terms to describe gas exchange are **CO\textsubscript{2} elimination** and **O\textsubscript{2} uptake**. Their ratio is called **respiratory exchange ratio**.

For sake of simplicity, and according to general practice, RQ is used to describe the ratio of measured quantities in this presentation, i.e. steady state conditions are always assumed.

**Figure 5** A scheme showing the role of the CO\textsubscript{2} and O\textsubscript{2} pools of the body in gas exchange
5.2 RQ of common substrates

The stoichiometric equations for chemical reactions connected with burning of particular substrates define the RQ and energy release of the reaction. For example, oxidation of glucose yields the following reaction:

\[
C_6H_{12}O_6 + 6O_2 \Rightarrow 6H_2O + 6CO_2 + 673 \text{ kcal (9)}
\]

The RQ is obviously 1.00. Since the volume of 6 moles of oxygen is 6 \times 22.4 liters (STPD) = 134.4 liters (STPD), the caloric value of O\textsubscript{2} in this reaction is 5.01 kcal/liter O\textsubscript{2}. One can also see that since one mole of glucose weighs 180 g, the oxidation of 1 g of glucose requires 0.746 L of O\textsubscript{2} and produces 0.746 L of CO\textsubscript{2} and 3.74 kcal of energy.

The fuels used by the body are carbohydrate, fat and protein. Proteins have different ratios of amino acids. A common procedure has been to use the heat of reaction and gas exchange values obtained from calorimetric measurement of the oxidation of lean beefsteak. The protein breakdown can be quantified by measuring the total amount of nitrogen liberated. The RQ commonly used for protein is 0.809.

Fat is usually assumed to be an equal mixture of palmitate, stearate and oleate, written as C\textsubscript{55}H\textsubscript{104}O\textsubscript{6}. It is oxidized according to stoichiometric equation

\[
C_{55}H_{104}O_6 + 78 O_2 \Rightarrow 55 CO_2 + 52 H_2O + 8135 \text{ kcal (10)}
\]

The RQ for fat is 0.71. Its caloric value is 9.46 kcal/g which is more than twice that of other substrates.
5.3 Substrate oxidation

When stoichiometric equations or caloric values and equivalent gas volumes are known, it is easy to write equations combining oxidation rate of a substrate with $O_2$ consumption and $CO_2$ production. In addition, an equation combining urea nitrogen production ($U_N$) with protein oxidation rate ($dP$) is needed:

$$dP = 6.25 U_N$$ (11)

The calorimetric values given in literature vary /27, 33-35, 40/. Typical values are given in Table 1.

### Table 1 Calorimetric values associated with oxidation of common substrates and production of urinary nitrogen.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Gas volume equivalent of 1 g of substrate (L)</th>
<th>Caloric value (kcal/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$O_2$</td>
<td>$CO_2$</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>0.829</td>
<td>0.829</td>
</tr>
<tr>
<td>Fat</td>
<td>2.019</td>
<td>1.427</td>
</tr>
<tr>
<td>Protein</td>
<td>0.966</td>
<td>0.782</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>6.04</td>
<td>4.89</td>
</tr>
</tbody>
</table>

Greatest variation is found in the caloric values. Values 4.1, 9.3 and 4.1 for carbohydrate, fat and protein, respectively, are used by some authors.

Combining the data from Table 1, we can immediately write equations relating $v_{O_2}$ and $v_{CO_2}$ with substrate oxidation rates:

$$v_{O_2} = 0.829 \text{CHO} + 2.019 \text{F} + 6.04 \text{U}_N$$ (12)

$$v_{CO_2} = 0.829 \text{CHO} + 1.427 \text{F} + 4.89 \text{U}_N$$ (13)

By solving these equations, for carbohydrate (CHO) and fat (F) oxidation rates equal to:

$$\text{CHO} = 4.12 v_{CO_2} - 2.91 v_{O_2} - 2.54 U_N$$ (14)
\[ F = 1.69 \nu_{O_2} - 1.69 \nu_{CO_2} - 1.94 \nu_N \]  \hspace{1cm} (15)

Protein oxidation rate is simply obtained from Equation (11).

Energy production rate, which is equal to energy expenditure (EE) in steady state, is obtained by taking the sum of oxidation rates multiplied by the caloric value of each substrate

\[ EE = 4.18 \nu_{CHO} + 9.46 F + 27 \nu_N \]  \hspace{1cm} (16)

By substituting CHO and F by (14) and (15) we obtain

\[ EE = 3.82 \nu_{O_2} + 1.22 \nu_{CO_2} - 199 \nu_N \]  \hspace{1cm} (17)

Because of differences in calorimetric values used, Equation (17) differs somewhat from the classical de Weir equation /32/ which is

\[ EE = 3.94 \nu_{O_2} + 1.11 \nu_{CO_2} - 2.17 \nu_N \]  \hspace{1cm} (18)

If values in the normal physiological range are used in these equations, results from (17) and (18) differ by less than one per cent. Assuming, e.g., \( \nu_{O_2} = 250 \) ml/min, \( \nu_{CO_2} = 200 \) ml/min and \( \nu_N = 13 \) g/d we get from Equation (17): \( EE = 1701 \) kcal/d and from Equation (18): \( EE = 1710 \) kcal/d.

Equations (12) to (17) will have somewhat different coefficients if values of pure glucose oxidation from Equation (9) are used in Table 1 instead of those of a typical carbohydrate.

According to the units used in Table 1, the units of Equations (12) to (17) will be liters/day for gases and grams/day for substrates. The conversion for gas units in ml/min is obtained by multiplying coefficients in front of \( \nu_{O_2} \) and \( \nu_{CO_2} \) by a factor 1.44. Then (17) becomes

\[ EE \text{ (kcal/day)} = 5.50 \nu_{O_2} \text{ (ml/min)} + 1.76 \nu_{CO_2} \text{ (ml/min)} - 1.99 \nu_N \text{ (g/day)} \]  \hspace{1cm} (19)
5.4 Predicted energy expenditure

The energy expenditure measured from a fasting, rested subject in the early morning in a darkened quiet room while completely at rest and in the recumbent position is called basal energy expenditure (BEE). The energy needed by a hospitalized patient can be called resting energy expenditure (REE) and it includes, in addition to the BEE, the energy required for eating and minimal physical activity and the thermogenic effect of food. The calculation of an individual’s predicted basal energy expenditure is usually based on body weight, height, age and sex. The most commonly used equations are based on the classical study by Harris and Benedict /36/made in 1919. The Harris-Benedict formulas for the basal energy expenditure (BEE) of males and females are as follows:

\[
\text{BEE (male)} = (66 + 13.8W + 5H - 6.8A) \text{ kcal/24h} \quad (20)
\]

\[
\text{BEE (female)} = (655 + 9.6W + 1.8H - 4.7A) \text{ kcal/24h} \quad (21)
\]

The Harris-Benedict formulas have been re-evaluated in several studies. Even if there is some variation in the results, the general conclusion seems to be /37-39/ that Harris-Benedict overestimates BEE by about 10%. This means that it would be more reasonable to interpret the Harris-Benedict formulas to represent REE instead of BEE.

5.5 Non-protein RQ

If protein oxidation is separated from Equations (12) and (13), one obtains non-protein \(v_{O2}^{\text{np}}\) \((np_{vO2})\) and \(v_{CO2}^{\text{np}}\) \((np_{vCO2})\), as well as non-protein RQ \((npRQ)\).

\[
np_{vO2} = v_{O2} - 6.04 U_N \quad (22)
\]

\[
np_{vCO2} = v_{CO2} - 4.89 U_N \quad (23)
\]

\[
npRQ = \frac{np_{vCO2}}{np_{vO2}} = \frac{v_{CO2} - 4.89 U_N}{v_{O2} - 6.04 U_N} \quad (24)
\]

The non-protein RQ changes linearly from 0.71 to 1.00 when
the mutual ratio between carbohydrate and fat oxidation goes from 0 to 100%. In the case when the non-protein RQ is greater than 1.00, or smaller than 0.71, some other biochemical phenomena, in addition to oxidation are present. Lipogenesis, i.e. lipid synthesis from glucose or protein, makes npRQ higher than one. Values of npRQ lower than 0.71 may be caused by gluconeogenesis or ketone metabolism. In these cases, the data obtained from indirect calorimetry alone is usually not enough for complete analysis of all the processes involved. For details see ref /27, 40/. 
6 CLINICAL RANGE OF MEASURED VARIABLES

Normal values for \( v_O2 \) and \( v_CO2 \) vary according to the body size, age and sex of the patient. Rough estimates of the values can be obtained from the formulas for predicted resting energy expenditure, e.g. the Harris-Benedict formula. If an age range from 20 to 80 years, height range from 150 to 190 cm, and weight range from 50 to 90 kg is assumed, the predicted \( v_O2 \) varies from 2.5 to 4.0 ml/kg/min and the \( v_CO2 \) from 2.1 to 3.4 ml/kg/min.

**Table 2 Normal values for \( v_O2 \) and \( v_CO2 \) according to the Harris-Benedict formula**

<table>
<thead>
<tr>
<th>SEX</th>
<th>AGE (yrs)</th>
<th>BODY WEIGHT (kg)</th>
<th>HEIGHT (cm)</th>
<th>( v_O2 ) (ml/kg/min)</th>
<th>( v_CO2 ) (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>20</td>
<td>50</td>
<td>150</td>
<td>4.0</td>
<td>3.4</td>
</tr>
<tr>
<td>male</td>
<td>80</td>
<td>50</td>
<td>150</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>male</td>
<td>20</td>
<td>90</td>
<td>190</td>
<td>3.5</td>
<td>2.9</td>
</tr>
<tr>
<td>male</td>
<td>80</td>
<td>90</td>
<td>190</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>female</td>
<td>20</td>
<td>50</td>
<td>150</td>
<td>3.9</td>
<td>3.3</td>
</tr>
<tr>
<td>female</td>
<td>80</td>
<td>50</td>
<td>150</td>
<td>3.1</td>
<td>2.6</td>
</tr>
<tr>
<td>female</td>
<td>20</td>
<td>90</td>
<td>190</td>
<td>2.9</td>
<td>2.5</td>
</tr>
<tr>
<td>female</td>
<td>80</td>
<td>90</td>
<td>190</td>
<td>2.5</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Table 2 is based on the assumption of oxidation of carbohydrate, fat, and protein in a 40:40:20 ratio (RQ = .84).

The increase in REE will cause an increase in both \( v_O2 \) and \( v_CO2 \). The magnitude of this increase can be estimated and will be reflected as similar increase in \( v_O2 \); the increase in \( v_CO2 \) tends to be slightly less due to the tendency of increased fat oxidation, and hence, lower RQ, in stress /11, 20, 21/.
Table 3  Change in resting energy expenditure due to clinical condition

<table>
<thead>
<tr>
<th>CLINICAL CONDITION</th>
<th>PERCENT CHANGE IN REE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional depletion or prolonged fasting</td>
<td>-10...-20 %</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>+0...+25 %</td>
</tr>
<tr>
<td>Fever (per °C above 37°C)</td>
<td>+10 %</td>
</tr>
<tr>
<td>Major trauma</td>
<td>+10...+40 %</td>
</tr>
<tr>
<td>Severe infection</td>
<td>+10...+30 %</td>
</tr>
<tr>
<td>Sepsis</td>
<td>+20...+60 %</td>
</tr>
<tr>
<td>Extensive burn injury</td>
<td>+50...+150 %</td>
</tr>
</tbody>
</table>

Temporary increases up to 200 % can occur due to shivering and convulsions. Hemodynamic catastrophies, such as circulatory collapse, may acutely reduce gas exchange due to impaired transport of O₂ and CO₂ between the tissues and the lungs. Once circulation has been adequately restored, a rebound increase will be observed.

Hyperventilation will acutely increase the $v_{CO2}$, and hypoventilation decrease it. Once the body store of CO₂ stabilizes to the new level of ventilation, $v_{CO2}$ will be the same as before the ventilatory change.

The physiological range of RQ is usually between 1.0 and 0.7. Large intakes of carbohydrate in excess to the REE may induce net lipogenesis, with a concomitant increase in RQ above 1.0. Even in this case, the RQ rarely exceeds 1.3 and an RQ significantly above 1.0 should be explored for measurement errors, before the interpretation of net lipogenesis is accepted. Similarly, an RQ below 0.7 is a rarity, but may occur during ketosis, if the ketone bodies are incompletely oxidized and excreted into the urine. Even in these conditions, the RQ rarely goes below 0.67 and an RQ below 0.7 should be explored for measurement errors /12, 27/.

Hyperventilation can elevate the RQ above 1.0, and correspondingly, hypoventilation can decrease RQ below 0.7. Analogously, when an oxygen debt develops, the RQ will increase and when the oxygen debt is paid, the RQ will decrease.
7 METHODOLOGICAL CONSIDERATIONS

7.1 Fick principle

An alternative for the gas exchange measurement of \( \dot{V}_O_2 \) and \( \dot{V}_C_O_2 \) is the use of the Fick principle. The Fick method calculates uptake or production of any substance as the arteriovenous content difference multiplied by flow. For \( \dot{V}_O_2 \), this can be done relatively easily, especially in the intensive care environment, if a clinical oximeter for the measurement of blood oxygen content is available \(/12, 41/\). Blood samples are taken from the pulmonary artery (mixed venous blood) and a systemic artery and the oxygen contents are measured. Cardiac output is usually measured with the thermodilution technique and the \( \dot{V}_O_2 \) calculated as arterial-mixed venous oxygen content difference multiplied by cardiac output. In principle, \( \dot{V}_C_O_2 \) could be measured with the same approach. However, measurement of blood CO\(_2\) content is complicated and not routinely available, and the Fick principle is therefore not used for \( \dot{V}_C_O_2 \) measurement.

The disadvantages of the Fick method include that it requires pulmonary artery catheterization and is therefore invasive, it is intermittent and gives only a spot value of \( \dot{V}_O_2 \), and the results are not immediately available. The most common method for cardiac output measurement, thermodilution, has large variability and may induce a significant error in the results.

7.2 Indirect calorimetry techniques

The main advantages of indirect calorimetry are non-invasiveness and the continuous monitoring of gas exchange that is possible with modern equipment. Two basically different techniques have been developed: the closed circuit and the open circuit techniques.

7.2.1 Close circuit technique

In the closed circuit, the subject breathes from a closed gas mixture, which can be either pure oxygen or an air-oxygen mixture. Carbon dioxide and water from the expiratory gases are removed and the same gas is used for subsequent inspirations. Oxygen is added to the circuit so that the original oxygen content is maintained. The added amount of oxygen corresponds to the \( \dot{V}_O_2 \). Measurement of \( \dot{V}_C_O_2 \) in the closed circuit requires measurement of flow and CO\(_2\) concentration as in the open circuit method.
7.2.2 Open circuit technique

In the open circuit method the expired gases are collected, the volume or flow of gas measured, and the inspiratory and expiratory concentrations of oxygen and carbon dioxide analyzed. $v_{O_2}$ and $v_{CO_2}$ are calculated from this data. Both the inspiratory and expiratory flow must be measured, or, more commonly, one of the flows measured and the other estimated using the Haldane transformation. The Haldane transformation assumes that only $O_2$ and $CO_2$ are exchanged in the lungs and the rest of the respiratory gases (excluding water vapour) have the same volume in both inspiratory and expiratory gases. When the inspiratory and expiratory concentrations of $O_2$ and $CO_2$ and either one of the flows are known, the remaining flow can be calculated. Most of the modern open circuit techniques use the Haldane transformation.

7.2.3 Open vs. closed circuit technique

The advantage of the closed circuit technique is that no measurement of oxygen concentration or flow for $v_{O_2}$ is required. Flow measurement is necessary for the $v_{CO_2}$ also in the closed circuit. The disadvantages are a complex breathing circuit, especially if use in mechanically ventilated patients is desired, vulnerability to even small leaks in the circuit, added resistance and compressed gas volume, especially during mechanical ventilation, the necessity to readjust ventilator settings, and the error caused by changes in end-expiratory lung volume.

The advantages of the open circuit method include lack of additional resistance and compressible volume and essentially simpler breathing circuit (canopy, mask, or mouthpiece in the spontaneously breathing patient and collection of expiratory gases in the mechanically ventilated patient). Insensitivity to changes in lung volume is an additional advantage. Accurate measurement of gas concentrations and volume or flow is the basis of this method.

The subsequent discussion will focus on the open circuit technique of indirect calorimetry.
7.2.4 Spontaneous breathing

Measurement of gas exchange in the spontaneously breathing patients should preferably be performed with a canopy system, since masks and mouthpieces induce changes in breathing pattern and may cause anxiety and discomfort, leading to erroneous results. Especially hyperventilation is common with masks and mouthpieces. When a canopy is used, large total flow of gas is needed in order to avoid CO₂ accumulation within the canopy. The commonly used flows are in the order of 40 L/ min. The high flow dilutes the expiratory gases and the gas concentration differences that have to be measured are small. Therefore all the available systems have been designed for the use of ambient air in the canopy measurement. Elevated inspiratory oxygen concentration in canopy measurement would make the concentration difference extremely small and the results prone to error.

7.2.5 Mechanical ventilation

Gas exchange measurement in the mechanically ventilated patient is a challenge and requires attention to detail. The most important potential sources of error are:

1. High pressures in the respirator circuit; PEEP, peak and mean pressure may all influence the gas analyzers.

2. High inspiratory oxygen concentrations (above 60 %) will increase the sensitivity of the Haldane transformation to error.

3. Instability of the inspiratory concentration of oxygen caused by the gas mixer or pressure fluctuations in the hospital’s compressed gas circuits.

4. Leaks in the respirator-patient circuit.

5. Temperature and humidity.

The error caused by high airway pressures can only be avoided by proper instrument design. It is extremely important that the system has been validated in conditions that match the extremes of its clinical use.

In practice, the open circuit method is not suitable for inspiratory oxygen concentration above 60 %. If an effort is made to minimize all the other sources of error and sufficiently long sampling periods are used, it may be possible to get reasonably reliable results up to inspiratory oxygen concentrations of 75 to 80 %.
The inspiratory oxygen concentration can be stabilized by use of a mixing chamber (the humidifier of the respirator is often suitable for this purpose) or by a pressure regulator between the hospital gas circuit and the respirator. If this is done, care should be taken that the pressure and the flow are still sufficient for the function of the gas mixer.

Meticulous care should be taken to avoid leaks in the respirator patient circuit. Common sites of leaks include the endotracheal tube, patient-respirator connectors and humidifiers.

The effects of temperature and humidity should be taken into account in the instrument design.

Figure 6  $F_{102}$ variation during various modes of mechanical ventilatory support

The variation coefficient of the $F_{102}$ during controlled mechanical ventilation, SIMV, and CPAP in 10 patients is shown in Figure 6. A reduction in the stability of $F_{102}$ during the modes including spontaneous breathing is obvious.
7.2.6 Intermittent mandatory and assisted ventilation

Use of intermittent mandatory ventilation (IMV) and other techniques of assisted ventilation will often create problems in the interpretation of the results. Firstly, the $F_{O_2}$ of the ventilator may vary more with these ventilation modes than during controlled ventilation. This variation is difficult to avoid but the error induced by this can be minimized by prolonging the measurement, i.e. by increasing the sample size. An additional mixing chamber for the inspiratory gases may also be used, if judged necessary.

Secondly, variation in the patient's breathing pattern may create both rapid and slow sequence variation in the concentration of the expiratory gases, which in turn increases the variability of the results. This variation is physiological since the varying breathing pattern induces fluctuation in the body pool of $CO_2$. The effect of this fluctuation can be minimized by increasing the sample size and a valid average of $v_{CO_2}$ and $v_{O_2}$ will usually be obtained within 30 - 60 minutes.

![Graph showing $v_{O_2}$ and $v_{CO_2}$ during different modes of mechanical ventilatory support](image)

Figure 7  $v_{O_2}$ and $v_{CO_2}$ during different modes of mechanical ventilatory support (see text, page 26)
A clinically stable patient with stable end-tidal and blood CO₂ concentrations is switched from synchronized intermittent mandatory ventilation (SIMV, frequency 6/min, Vₜ .8 L) to controlled mechanical ventilation (arrow 1 in Figure 7) with the same Vₜ and total ventilation, and after 30 min to spontaneous ventilation with continuous positive airway pressure (CPAP, arrow 2). The two main reasons for the variation of v.O₂ and v.CO₂ during the SIMV and CPAP are variation in the breathing pattern, which causes fluctuation in the mixed expiratory gas concentrations and in the alveolar gas concentrations, and variation in the FIO₂ caused by the gas blender of the ventilator (see Figure 6). Prolonged sampling periods in order to obtain a representative mean value are necessary.

7.2.7 Interrelation of ventilation and the measurement of gas exchange

Minute ventilation has a fundamental effect on the measurement of gas exchange, since it determines the dilution of the CO₂ and O₂ concentrations in the mixed expiratory gases. The actual demand for ventilation varies widely due to pulmonary factors and the desired arterial blood gases. Hence, the expiratory CO₂ and O₂ concentrations at a given level of v.CO₂ and v.O₂ may also vary widely.

This interrelation of ventilation and gas exchange measurement is demonstrated by considering the effects of dead space ventilation and arterial PaCO₂ on the ventilatory demand and the expired CO₂ concentration (calculations according to Equation (7)):

### Table 4 Effect of dead space and arterial PaCO₂ on minute ventilation and expired CO₂ concentration

Assume v.CO₂ = 150 ml/min

<table>
<thead>
<tr>
<th>Effect of ( \frac{V_D}{V_T} )</th>
<th>( p_{aCO₂} ) (kPa)</th>
<th>( \frac{V_D}{V_T} )</th>
<th>( V_E ) (L/min)</th>
<th>( F_{ECO₂} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of ( \frac{V_D}{V_T} )</td>
<td>5.3</td>
<td>0.25</td>
<td>4.6</td>
<td>3.26</td>
</tr>
<tr>
<td></td>
<td>5.3</td>
<td>0.75</td>
<td>13.9</td>
<td>1.08</td>
</tr>
<tr>
<td>Effect of low ( p_{aCO₂} )</td>
<td>3.5</td>
<td>0.25</td>
<td>7.0</td>
<td>2.14</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>0.75</td>
<td>21.0</td>
<td>0.71</td>
</tr>
<tr>
<td>Effect of high ( p_{aCO₂} )</td>
<td>8.0</td>
<td>0.25</td>
<td>31</td>
<td>4.84</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>0.75</td>
<td>9.2</td>
<td>1.63</td>
</tr>
</tbody>
</table>
This clinically relevant example results in the range of $F_{ECO2}$ of 0.71 - 4.84 %. Assuming a $F_{IO2}$ of 0.40, the corresponding range of expired $O_2$ concentration at a $v_{O2}$ of 150 ml/min would be 35.16 - 39.29 %. Accordingly, instrument design and validation should take into account the spectrum of clinical conditions resulting in the wide range of expired gas concentrations.
Indirect calorimetry realized with an open gas system is characterized by the calculation of gas exchange from gas concentrations and flow data. No external means, e.g. CO$_2$ absorber, are added to interfere with the natural measurement set-up. The techniques used in O$_2$, CO$_2$ and flow measurement are described in the following chapters.

The open system configuration depends on whether artificially ventilated or spontaneously breathing patients are measured. The basic alternatives are presented in Figures 8a-c.

**Figure 8a** Basic open system measurement configuration with mixing chamber for mechanically ventilated patients

**Figure 8b** Open flow-through canopy system for spontaneously breathing patients
The advantage of the breath-by-breath measurement is faster system response time, but, on the other hand, it is technically much more demanding than the mixed gas approach. The main difficulties are associated with synchronization of gas and flow signals /42/. Breath-by-breath systems have gained some popularity in dynamic stress-test measurements, but in rest state measurements the true physiological changes are so slow that the more reliable mixing chamber method is preferred by most researchers.

Figure 8c  Breath-by-breath system for both spontaneously breathing and mechanically ventilated patients
8.1 Haldane transformation

The precise way to measure $O_2$ consumption requires measurement of both inspiratory and expiratory gas volumes and $O_2$ concentrations.

\[ V_{CO2} = F_{IO2} \cdot V_I - F_{EO2} \cdot V_E (25) \]

If no other gases than $O_2$, $CO_2$ and $N_2$ are present and if no nitrogen exchange is assumed, the difference between $V_I$ and $V_E$ can be calculated and it is necessary to measure only $V_I$ or $V_E$. Their difference is equal to the difference between $V_{CO2}$ and $V_{O2}$, and is usually of the order of a few tens of milliliters/min. If $RQ = 1$ then $V_{CO2} = V_{O2}$ and $V_I$ is exactly equal to $V_E$. Measurement of both volumes accurately enough is practically impossible, the only practiced way is to calculate the difference with an algorithm called the Haldane transformation. As a curiosity, if it were possible to measure $V_I - V_E$, no $O_2$ measurement would be needed, since $V_{O2}$ could be obtained from $V_{CO2}$ and ($V_I - V_E$).

Assuming no nitrogen exchange in the lungs:

\[ F_{IN2} \cdot V_I = F_{EN2} \cdot V_E (26) \]

\[ (1 - F_{IO2}) \cdot V_I = (1 - F_{EO2} - F_{ECO2}) \cdot V_E (27) \]

Here, for simplicity, $F_{ICO2}$ was assumed to be zero. Then by substituting $V_I$ from (27) into (25) we obtain:

\[ V_{O2} = (F_{IO2} \frac{1 - F_{EO2} - F_{ECO2}}{1 - F_{IO2}} - F_{EO2}) \cdot V_E (28) \]

Manipulating further, this can be written as:

\[ V_{O2} = (\frac{F_{IO2} - F_{EO2}}{1 - F_{IO2}}) \cdot V_E (29) \]
The CO\textsubscript{2} production can be obtained by starting from:

\begin{equation}
\dot{v}_{\text{CO2}} = F_{\text{ECO2}} \cdot \dot{v}_E - F_{\text{ICO2}} \cdot \dot{v}_i
\end{equation}

(30)

Again by substituting \(\dot{v}_i\) from (27) into (30), we obtain:

\begin{equation}
\dot{v}_{\text{CO2}} = [F_{\text{ECO2}} - F_{\text{ICO2}} \left( \frac{1 - F_{\text{EO2}} - F_{\text{EICO2}}}{1 - F_{\text{IO2}}} \right)] \cdot \dot{v}_E
\end{equation}

(31)

Since \(F_{\text{ECO2}}\) is usually some 4 \% and \(F_{\text{ICO2}}\) around 0.05 \% and since the multiplier of \(F_{\text{ICO2}}\) in Equation (31) is close to one, a negligible error is introduced by replacing Equation (31) with

\begin{equation}
\dot{v}_{\text{CO2}} = (F_{\text{ECO2}} - F_{\text{ICO2}}) \cdot \dot{v}_E
\end{equation}

(32)

It is also quite common to ignore \(F_{\text{ICO2}}\) in Equation (32). One has to note that during mechanical ventilation \(F_{\text{ICO2}}\) is smaller than the ambient CO\textsubscript{2} content, since the inspiratory gas is made by mixing air with pure oxygen which does not contain CO\textsubscript{2}. Assuming \(F_{\text{ECO2}}\) level of 4 \% and \(F_{\text{ICO2}}\) level of 0.04 \%, a relative error of 1 \% is introduced by neglecting \(F_{\text{ICO2}}\). Since errors from several sources will be accumulated in the final results of metabolic quantities, it is good practice to try to eliminate all possible contributors even if they alone seem small. So Equation (32) should be used without dropping \(F_{\text{ICO2}}\).

The effect of \(F_{\text{ICO2}}\) is naturally much more dominant when diluted CO\textsubscript{2} concentrations are measured, as is done in the canopy measurements.

8.2 Oxygen measurement

8.2.1 Electrochemical O\textsubscript{2} sensor

The most popular oxygen sensor in routine measurements is the polarographic sensor using liquid electrolyte (see Figure 9). It is also called Clark-electrode according to the inventor Leland C. Clark. In this type of sensor, oxygen molecules have to diffuse through a thin teflon membrane into the electrolyte which is usually potassium chloride. Then, an electric current proportional to the oxygen partial pressure will be generated between the platinum cathode and silver anode. The response
time of the sensor depends on the thickness of the membrane and is usually not rapid enough to follow breath-by-breath $O_2$ variations.

![Figure 9 Construction of a polarographic cell](image)

Another modification of the electrochemical principle is the fuel cell. It has gold cathode and lead anode in a potassium hydroxide electrolyte. No external voltage is needed since the cell itself acts as a battery.

Because of the working principle based on the “burning” of the electrolyte the life time of the electrochemical cell is limited and depends on the oxygen level of the gas it is exposed to. In the fuel cell the relationship is straightforward and the life time can be specified as $O_2$ per cent hours. A cell with a thin membrane and fast response is usually more unstable and has a short lifetime.

The linearity of the polarographic sensor has caused problems in indirect calorimeter applications. These cells show nonlinearity at high $O_2$ concentrations and their linearity may also change towards the end of their life time. Because of the working principle, refilling of the electrolyte is needed as routine maintenance. In the optimum case, life times of half a year are typical.

An alternative to the liquid electrochemical sensor is a solid state cell using zirconium dioxide as electrode material. These cells typically work in 700-800°C temperature range which makes their use hazardous if anaesthetic agents are present.
Zirconium cells are fast, having a typical response time of 100 ms. The cell life time is about one year. A linearizing circuit is needed since this cell has a logarithmic characteristic curve.

8.2.2 Paramagnetic $O_2$ sensors

Oxygen is a gas having magnetic susceptibility more than hundred times greater than other common respiratory gases. A gas with a positive susceptibility is called paramagnetic while one with a negative susceptibility is diamagnetic. Numeric values for the relative magnetic susceptibilities of the most relevant respiratory gases are given in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>Relative magnetic susceptibilities of respiratory gases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>100</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>-0.35</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>-0.64</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>-0.57</td>
</tr>
</tbody>
</table>

The paramagnetic property has been used for oxygen measurement in various measuring cell configurations. The basic physical mechanism making this measurement possible is that oxygen molecules experience a force in a nonhomogeneous magnetic field. In the field gradient the molecules tend to move to the direction where the field is higher.

The classical paramagnetic analyzer is based on Pauling’s principle /43/ where a torsional effect upon a dumbbell suspended in a nonhomogeneous magnetic field is measured using an optical lever technique. Because of relatively large volume of the measuring cell these analyzers have slow response time /44/. They are also mechanically sensitive so that a moderate mechanical shock may damage the sensor.

A rapid response paramagnetic $O_2$ sensor was first constructed by Hummel /45/. In this sensor type, a pressure signal generated by $O_2$ molecules in a chopped, nonhomogeneous magnetic field is measured (see Figure 10). According to the physical laws associated with the interaction between magnetic field and oxygen molecules, a pressure difference exists between the gas outside the field and the gas inside the field. This pressure difference is proportional to the partial pressure of oxygen in the gas. Assuming the two gases to be measured
to contain 100 % and 21 % O₂, the mixture contains 60.5 % O₂. Starting from the outlet at point C (Figures 11a-c) the pressure inside the field is 60.5 units higher.

By following the routes CBA and CBD the pressure at points A and D can be found to be 60.5 - 100 = -39.5 units and 60.5 - 21 = 39.5 units, respectively. The output of the pressure transducer is P_D - P_A = 39.5 - (-39.5) = 79 units, which is equal to the O₂ concentration difference between the gases to be measured. The commercial analyzers based upon this principle (Rapox by Godard and Oxytest S by Hartmann and Braun) were not successful because of problems caused by external noise, vibrations and pressure effects of mechanical ventilators /46/.

The Hummel approach was developed further by Meriläinen, /47, 48/ introducing a new mechanical design for the measuring cell and integrating pneumatic filters into a construction of compact size. This sensor with a response time of 150 ms has been commercially manufactured since 1985 (OM-101 by Datex).

Figure 10  Working principle of a fast differential O₂ sensor
Figure 11a Differential $\text{O}_2$ sensor. Perpendicular cross section of the air gap of an electromagnet.

Figure 11b Pneumatic bridge of a differential $\text{O}_2$ sensor. Changes in pressure along route ABC when field is switched on (solid line) and off (dashed line).
The main problems in the design of these analyzers have been related to magneto-mechanical effects. The strong chopped magnetic field generates vibration in the measuring cell which means a pressure signal in-phase with the effective $O_2$ signal to be measured. These effects may generate temperature drifts and common-mode effects for the differential measurement. The fast response time of the sensor, however, allows automatic compensation of these effects during the measurement.

8.3 $CO_2$ measurement

Carbon dioxide is most often measured by using infrared absorption technique (see Figure 12). $CO_2$, as well as asymmetric molecules in general absorbs infrared radiation of a specific wavelength. The wavelength used for $CO_2$ analysis is 4.3 µm. The infrared measurement technique is well established. It has nonlinear characteristic so that linearization is required. Precision requirements of the standard capnometry application are not very strict, but special attention has to be paid on the accuracy of the linearization in metabolic measurements. Especially when diluted $CO_2$ concentrations with 0.5...1 % $CO_2$ have to be measured, even a deviation of 0.01 % in linearization means a relative error which can not be ignored. It is also important to fix the true zero of the characteristic curve by calibration with a $CO_2$-free gas. Failure to do this, e.g. by zeroing with room air, will also be reflected in gain calibration because of nonlinearity.
Another problem with the infrared CO$_2$ sensor is its cross-sensitivity to other gases. The peak width of the spectral absorption line is affected by collision broadening effect due to other molecules and with a fixed filter window this means change of output signal. In practice at least the cross-sensitivity for nitrogen and nitrous oxide has to be compensated.

8.4 Multigas analysers

In addition to the methods mentioned above a mass-spectrometer can be used to measure both oxygen and carbon dioxide. Mass-spectrometer has some disadvantages which makes its use in routine metabolic measurements less attractive. They are big and expensive, and a dedicated technician may be needed to ensure reliable performance of the apparatus.

A multigas analyzer based on the Raman scattering of laser light is under development /49/ and may become a serious alternative for separate gas sensors.
The most commonly used flow meters are pneumotachographs, turbines, hot-wire anemometers, ultrasonic and vortex flow meters. The details of their working principles are beyond the scope of this book. Instead we discuss some general problems associated with most flow meters.

In ideal conditions, with static flows and dry and clean gases, all these sensors can exhibit good accuracy and reproducibility, but unfortunately when human respiratory flow is measured in real clinical conditions, they often work in an unsatisfactory way. The main reasons for this are the effects of humidity, saliva or mucus, alternating gas composition and the dynamic response of the sensor. Complicated compensation and calibration algorithms are needed to eliminate these effects. In addition, frequent cleaning of the sensor head is needed in most cases.

Calibration of the flow sensors is usually performed by pumping with a syringe of determined size. To cover dynamic effects the calibration should be made at several pumping rates. It should also be noted that room air pumping may not be adequate when wet gases with high O$_2$ concentration are to be measured.

An alternative to flow measurement is volume measurement by mechanical gas meters or gas bell spirometers.
One possibility to avoid problems with flow sensors is the use of the dilution method. If an unknown volume \( V_{CO_2} \) of CO\(_2\) is mixed with a known volume \( V \) of a gas with no CO\(_2\), the unknown volume can be calculated by measuring the CO\(_2\) concentration of the mixture. The diluted CO\(_2\) concentration is:

\[
F_{CO_2} = \frac{V_{CO_2}}{V + V_{CO_2}}
\]

Then the unknown \( V_{CO_2} \) is simply obtained as follows:

\[
V_{CO_2} = \frac{V \cdot F_{CO_2}}{1 - F_{CO_2}}
\]

In the same manner, an unknown CO\(_2\) flux can be calculated when it is mixed with a known flow of diluent gas.

The most convenient gas always available as diluent is ambient room air. Naturally the CO\(_2\) content of room air also has to be measured, since it can vary between 0.04...0.15 % depending on the number of persons, room size and quality of air conditioning. Variations in the water vapour content of the air also have to be considered if the ambient air is exceptionally hot and wet. The water vapour fraction may, or may not, be involved in the dilution process, depending on the gas drying method which is used.

If a constant flow generator with a flow \( Q \) is used, by using the configuration shown in Figure 13 the CO\(_2\) flux \( w_{CO_2} \) is:

\[
w_{CO_2} = (F_{CO_2} - F_{ICO_2}) \cdot Q
\]
Note that the constant flow generator keeps the output flow of the system fixed and independent of the added flux. The input flow is then $Q - w_{CO_2}$.

The amount of flow, $Q$, can either be measured with a flow sensor or determined indirectly by infusing a known amount of CO$_2$ into the air stream and setting the flow value so that the CO$_2$ production measured and calculated according to the Equation (35) will match with the flux infused.

The expired minute volume can be obtained with dilution method if a mixed expiratory gas flow is mixed with constant air flow as shown by Figure 14. If the CO$_2$ content of the gas before dilution is $F_{ECO_2}$ and after dilution $F_{DCO_2}$ (see Figure 14), the expiratory flow is then:

$$v_E = \frac{F_{DCO_2}}{F_{ECO_2}} \cdot Q$$  (36)
Figure 14  Dilution of mixed expired CO$_2$ with constant air flow

A complete metabolic gas exchange measurement system (Deltatrac$^\text{TM}$ Metabolic Monitor, Datex-Ohmeda) is based on the gas dilution principle /48/. In this system, multiplexed gas sampling is required for both CO$_2$ and O$_2$ measurement. Rapid response of the O$_2$ measurement is essential, in Deltatrac$^\text{TM}$ this has been achieved by using the paramagnetic O$_2$ sensor (OM-101 by Datex-Ohmeda). Deltatrac$^\text{TM}$ also effectively exploits the O$_2$ sensor's differential measuring principle.

The key component of this method is the constant flow generator. It must have good stability over a long time and its performance should be easy to check.
11 EFFECTS OF TEMPERATURE, PRESSURE AND HUMIDITY CONVERSIONS

The formula \( pV = nRT \) states the relationship between volume, pressure and temperature for an ideal gas. This means that when any gas volume is given, one always has to ask: at which pressure and temperature? In addition, water vapour is always present in respiratory gases, so one must also ask if the volume in question is the total volume or the dry gas volume.

The respiratory gas volumes are usually given in STPD, ATPD or BTPS conditions.

\[ \text{STPD} = \text{standard temperature (0°C = 273K) and pressure (760 mmHg = 1013 mbar), dry gas} \]

\[ \text{ATPD} = \text{ambient temperature and pressure, dry gas} \]

\[ \text{BTPS} = \text{body temperature (37°C) and pressure (p-47 mmHg), gas saturated with water vapour (} P_{\text{H}_2\text{O}} = 47 \text{ mmHg}) \]

The conversion formulas between each pair of volumes can be obtained by using ideal gas law \( \frac{pV}{T} = \text{constant} \)

\[ V_{\text{STPD}} = \frac{p}{760} \cdot \frac{273}{273 + T} \cdot V_{\text{ATPD}} \quad (37) \]

\[ V_{\text{BTPS}} = \frac{273 + 37}{273} \cdot \frac{760}{p - 47} \cdot V_{\text{STPD}} \quad (38) \]

As a rough rule of the thumb, \( V_{\text{ATPD}} \) is 8...9 % more than \( V_{\text{STPD}} \) in normal ambient pressure conditions at sea level. If ambient pressure is high, this difference gets smaller. As to the \( V_{\text{BTPS}} \), the effect of thermal expansion makes it 13.5 % higher than \( V_{\text{STPD}} \), and the introduction of water vapour makes an additional 6 %. Taking all factors into account \( V_{\text{BTPS}} \) is some 20 % more than \( V_{\text{STPD}} \). At high altitudes, these ratios are naturally different.

In practice, volumes are usually measured under ambient conditions but it is conventional to give \( O_2 \) consumption and \( CO_2 \) production in STPD and minute ventilation \( \nu_E \) in BTPS.

In addition to the effects due to basic laws of physics of gases as shown above, there are a number of secondary physical
mechanisms which cause temperature, pressure and humidity to affect the results of gas exchange measurements.

A very important point to note is that most gas analyzers measure partial pressure instead of percentage or concentration. The partial pressure of a gas component is directly proportional to the number of molecules in a fixed volume. The sum of partial pressures of all the gas components has to equal the ambient pressure. In practice, this means that even if the air contains 20.93 % oxygen both at sea level and at an altitude of 1000 m, the absolute gas sensor output is usually some 10 % lower at 1000 m. In general, the relationship between partial pressure and sensor output is not necessarily linear. For this reason, experimentally verified pressure compensation algorithms are required to ensure accuracy at all relevant altitudes.

Water vapour has a direct effect upon the partial pressure measurement of a gas. At 25°C, a gas mixture can contain 3 % water vapour (100 % relative humidity) which means that 3 % lower value is obtained for the partial pressure of a gas mixture compared with a situation with a dry gas mixture. To correct this effect, measurement and calibration has to be made under identical humidity conditions. Since calibration gas from a bottle is dry, water should therefore be removed from the gas to be measured. Another possibility is to equalize humidities of both gases with the ambient air humidity. This is possible by using a special tubing material (Nafion, PermaPure Inc., N.J., USA) which is selectively permeable for water vapour.
SAMPLE GAS PRESSURE EFFECTS

Changes in ambient pressure is only one aspect of the effects of pressure on gas exchange measurements. In most of the gas measurement systems (except main-stream sensors), a tiny sample flow is continuously sucked through the sensors. So in practice, the pressure inside a gas sensor is somewhat lower than the ambient and this pressure may change during different phases of measurement or if the sampling pump power is not stable.

A special problem will arise when gas has to be sampled from a point having a fluctuating over-pressure compared to the ambient, as is the case in gas measurements from the inspiratory side of a mechanical ventilator. In addition to the direct effect through the change of partial pressure, gas sensors may have some specific pressure effects. For the compensation of all pressure effects, a pressure sensor has to be used to continuously measure the true pressure close to the measuring cell. The compensation coefficient has to be verified experimentally. The same pressure sensor can be used to measure ambient pressure if the sampling pump is stopped. Then all pressures inside the sampling system become equalized with the ambient.

The external over-pressure has the most serious effect upon the measurement of the inspiratory-expiratory oxygen difference in an open system. The expiratory O\textsubscript{2} is measured from the mixing chamber at ambient pressure, but inspiratory O\textsubscript{2} from a point with cyclically varying pressure, possibly with a static over-pressure component (PEEP). At high oxygen levels, the pressure compensation accuracy for inspiratory gas has to be very high to maintain accuracy of O\textsubscript{2} difference.

However, by using a differential O\textsubscript{2} sensor, the pressure effect is inherently much smaller. As an example, we can take the case of an inspiratory O\textsubscript{2} value of 50 % and a mixed expiratory value of 46 %. With an ordinary sensor when inspiratory and expiratory levels have to be measured individually, the pressure effect will change the inspiratory value but not the expiratory one. Assume a 10 cmH\textsubscript{2}O over-pressure, which means typically 1 % higher gain for the inspiratory measurement. Then, without any pressure compensation the measured value will be 50.5 %, instead of 50 %, and the oxygen difference 4.5 % instead of 4 %. This means a 12.5 % relative error for the O\textsubscript{2} difference, which is further magnified by the Haldane transformation algorithm as shown later. With a differential sensor the same over-pressure will cause a 4 % difference to 4.04 %, so the relative error of the difference is only 1 %. After a proper pressure compensation the errors naturally become smaller, but this example clearly shows that the
compensation requirement is much smaller for a differential sensor.

The sample gas pressure effects are also present in the breath-by-breath measurements, and their precise compensation is very difficult.
13 VALIDATION OF GAS EXCHANGE MEASUREMENTS

13.1 Calibration of gas transducers

It is clear from error analysis of gas exchange measurements (see Appendix B) that precise calibration of gas sensors is of crucial importance. The O\textsubscript{2} and CO\textsubscript{2} sensors can either be calibrated with a mixture of both gases or with separate gases.

13.1.1 O\textsubscript{2} calibration

The O\textsubscript{2} calibration philosophy depends on the type of sensor. If the linearity of the sensor is suspect, a two-point calibration should be made with gases close to the O\textsubscript{2} range where measurement is made. Ideally, the two gases should match the F\textsubscript{IO2} and F\textsubscript{EO2} level of the real measurement. In practice it is difficult and expensive to purchase a set of gases with precision good enough to cover a reasonable range for respirator measurements. For canopy measurements, where small differences from room air are measured, two very accurate gases should be used, since the room air O\textsubscript{2} concentration in the hospital environment is not always stable.

If the sensor linearity is good, it is always most convenient to use pure, hospital-grade oxygen and room air as the calibration gases. For gain calibration, it is not significant if the ‘pure O\textsubscript{2}’ varies between 99.8 and 100 % or if the room air O\textsubscript{2} concentration is 20.9 to 21.1 %. The error analysis of Equation (28) shows (see Appendix B) that the error sensitivity of the inspiratory-expiratory O\textsubscript{2} difference is much higher than that of the absolute value of F\textsubscript{IO2}. This means that the two-point calibration with room air and pure oxygen with somewhat uncertain values still ensures good accuracy for the (F\textsubscript{IO2} - F\textsubscript{EO2}) difference (see Figure 15).
Figure 15  O₂ sensor calibration curves with 20.9/100 % O₂ (curve 1) and 21.1/99.8 % O₂ (curve 2). The relative difference for measured results (Uₖₒ₂ - Uₖₑₒ₂) is (79.1 - 78.7)/78.7 = 0.5 %.

The same approach can be used for a differential O₂ sensor with good linearity. The electrical baseline of the differential sensor can easily be determined by connecting the two gas sampling lines to sample the same gas from a common point.

13.1.2  CO₂ calibration

The measuring range of a CO₂ sensor is usually 0...10 % of CO₂, so pure CO₂ cannot be used for calibration. Instead, a precise calibration gas within the range 3..5 % CO₂ is required. Because of some cross-sensitivity of infrared CO₂ measurement for other gases, it is important to realize that 5 % CO₂ in air or oxygen or nitrogen gives a different result and this effect has
to be compensated for both during calibration and measurement.

A convenient mixture to calibrate both CO\textsubscript{2} and O\textsubscript{2} sensor simultaneously is carbogen, with 4...5 \% CO\textsubscript{2} in oxygen. In this case, the N\textsubscript{2}/O\textsubscript{2} compensation of CO\textsubscript{2} measurement has to be precise to avoid errors. The baseline check of the CO\textsubscript{2} sensor should always be made through a CO\textsubscript{2} absorber (soda lime) or with a CO\textsubscript{2}-free gas, e.g. pure nitrogen. Even if the uncertainty of the room air CO\textsubscript{2} content, as such, does not seem significant in gain calibration with CO\textsubscript{2} on the level of 4...5 \%, the real effect is greater because of the nonlinearity of the CO\textsubscript{2} measurement. Quality of characteristic curve linearization is of great importance when small CO\textsubscript{2} fractions, (0.5 \%) as in canopy measurements, are measured, if the calibration is performed with 4...5 \% CO\textsubscript{2}. Methods to check the overall performance of gas measurements, including linearity, are described in Section 13.2.

13.2 Simulations

Gas sensor calibration properly performed with precise gases, is vital to ensure accurate gas exchange measurements. In principle, the final results cannot be better than the accuracy of the calibration gases. However, if the system as a whole can be checked with simulation and systematic deviations corrected, the opposite may be true.

13.2.1 Simulating $\dot{V}_{\text{O2}}$ and $\dot{V}_{\text{CO2}}$

An overall check of system performance can be made by simulating CO\textsubscript{2} production and O\textsubscript{2} consumption by infusing CO\textsubscript{2} and N\textsubscript{2} into the system, preferably into a test-lung configuration. CO\textsubscript{2} infusion $\dot{w}_{\text{CO2}}$ directly simulates CO\textsubscript{2} production:

$$\dot{V}_{\text{CO2}} = \dot{w}_{\text{CO2}}$$ (39)

Nitrogen infusion does not generate any real physical O\textsubscript{2} consumption, rather a O\textsubscript{2} difference which in gas exchange calculation formulas is equivalent to O\textsubscript{2} consumption (see Figure 16).
Figure 16  Infusion of N\textsubscript{2} flux into a gas flow.  
Note that there is no net O\textsubscript{2} consumption.

By using symbols defined in Figure 16, the O\textsubscript{2} concentration after dilution is:

\[ F_{E02} = F_{I02} \frac{V_1}{V_E} \frac{V_1}{V_1 + W_{N2}} \]  \hspace{1cm} (40)

Substituting this into (28), we obtain for the simulated O\textsubscript{2} consumption:

\[ \dot{V}_{O2} = \frac{F_{I02}}{1 - F_{I02}} \cdot \dot{W}_{N2} \]  \hspace{1cm} (41)

This simulation works well with room air when \( F_{I02} \) is known, but requires very accurate measurement of the absolute \( F_{I02} \) level at higher oxygen concentrations. For example, if 51 % is used in (41) instead of true value of 50 %, the predicted result from the same infusion will change 4.1 %. On the other hand, in real measurements oxygen consumption is actually very insensitive to the error of absolute \( F_{I02} \) if the O\textsubscript{2} difference is precise.
If CO₂ and N₂ are infused simultaneously, there should be no change in the resulting $v_{O_2}$ compared to N₂ infusion alone. This can be verified by, instead of (40), writing:

$$F_{EO_2} = F_{IO_2} \frac{v_I}{v_I + w_{N_2} + w_{CO_2}}$$

(42)

Substituting this into (28), and using $F_{ECO_2} = w_{CO_2} / v_e$ one obtains (41) again.

If CO₂ alone is infused, it should not produce any O₂ consumption. This can be seen by letting $w_{N_2} = 0$ in (42) and making the same manipulation as above.

### 13.2.2 Equipment for gas infusions

A constant gas flow can be generated by applying a constant pressure difference across a fixed flow resistance. The relevant infusion rates are 100 to 300 ml/min for CO₂ and 100 to 1200 ml/min for N₂. The flow resistance can either be of the orifice type or a thin metal tubing, e.g., a standard injection needle. A constant pressure difference of some 2 atmospheres has to be maintained across the flow restrictor by using a pressure regulator. To cover the whole range of relevant infusion rates, a set of flow restrictors and an adjustable pressure regulator are needed.

The stability of the infusion rate depends on both the quality of the pressure regulator and the properties of the flow restrictor. In practice, the combination of a great pressure difference with a small orifice produces a more stable and repeatable rate than the opposite configuration. A special advantage is achieved if the pressure is high enough and the orifice small enough to meet the criteria for a critical orifice condition /50/. Then the flow becomes independent of the downstream pressure, which is of importance when gas is infused into a test lung with varying pressure due to mechanical ventilation. It is, however, difficult to achieve the critical orifice criteria for all necessary flow rates and the back pressure problem generated by the ventilator can be eliminated as well by infusing the gas into the expiratory side of ventilator where back pressure is negligible.

A major practical problem with gas infusions is precise determination of the infusion rate. As a primary method a bell
type gasmeter or spirometer should be used for measurement of
the volume of the gas collected during a certain period of time.
Attention has to be paid to the optimal collection time compared
to the accuracy of reading the volume. Naturally, the ambient
pressure and gas temperature inside the bell has to be
measured. A high quality rotameter calibrated with the primary
method can also be used to measure the flow rate and follow its
stability.

Another method to directly obtain the mass or STPD infusion
rate is by following the weight decrease of the infusion gas
bottle with an electronic precision scale. Scales with a range of
4 kg and resolution of 10 mg are available. For CO$_2$ 10 mg means
a gas volume of about 5 ml. A disadvantage of this method is
that special, small-size gas bottles are needed.

Commercial mass flow controllers based on thermal principle
(e.g., Brooks) have good reproducibility and are convenient to
use, since infusion rate is electrically adjustable over a wide
range.

Altogether, the gas infusion validation, even if straightforward
in principle, requires extremely careful attention to the details
of technical aspects and it is questionable if it can be used as a
routine method in clinical surroundings. On the other hand, the
manufacturers of commercial gas exchange monitors should use
this method in routine quality assurance procedures.

13.2.3 RQ simulation

RQ alone, which is flow independent, can easily be validated by
burning methanol or ethanol in a system with a proper gas
collection configuration. For ethanol, the stoichiometric
equation is:

$$C_2H_5OH + 3O_2 \Rightarrow 2CO_2 + 3H_2O$$

Since 2 parts of CO$_2$ is produced and 3 parts of O$_2$ consumed,
RQ is 2/3 = 0.666. Acetone with RQ of 0.75 can also be used, but
more attention has to be paid to safety aspects. There are several
techniques in performing the alcohol burning test. First of all,
the liquid can be burned either in an open vessel or in a lamp
with a wick, and the burning rate can also be controlled if a
burner with a pump delivery is used.

The basic configuration of RQ simulation for flow-through
canopy case is shown in Figure 17 and for respirator setting in
Figure 18.
Figure 17 Configuration for RQ simulation by ethanol burning for flow-through canopy measurements

Figure 18 Configuration for RQ simulation by ethanol burning for respirator measurements

The canopy configuration is simple to use. The air flow shunt is needed for a lamp and wick of standard size to stabilize the flame and keep it small enough to match the relevant physiological range.
Burning alcohol in the respirator configuration is more problematic. Again the flame size has to be controlled by adjusting the shunt flow. The need for shunting depends on the oxygen level and minute ventilation. Some obvious safety aspects also have to be taken into account when elevated oxygen levels are involved. The burning always has to be started by ventilating with room air, which usually requires the shunt to be closed totally to maintain burning. Then, the O\textsubscript{2} level can be gradually increased by simultaneously opening the shunt and trying to maintain a proper flame size. If the flame is accidentally extinguished, the system has to be flushed, by ventilating with room air, before igniting again. After some training, RQ simulation by burning alcohol can be performed up to O\textsubscript{2} levels of 60 or 70 %. In principle, a burner with an adjustable infusion pump could be a more convenient alternative at high O\textsubscript{2} levels.

A special feature in alcohol burning, as can be seen from Equation (43), is that plenty of water vapour is also produced. In normal respiration the expired water vapour flow is some 5 % of the minute ventilation which normally means 300 to 500 ml/min. Since water vapour production in alcohol burning is, according to Equation (43), equal to O\textsubscript{2} consumption, it is clearly of the same order of magnitude as in normal breathing.

This means that as to the possible effects of humidity, ethanol burning is a more relevant test than infusion of dry gases. A separate humidifier can naturally be used with infusion, but it may be difficult to know the water evaporation rate.

13.2.4 Quantitative alcohol burning

In addition to defining RQ, alcohol burning can also be used in principle for checking absolute values of \( v_{\text{CO}_2} \) and \( v_{\text{O}_2} \). From stoichiometric equations and alcohol density data, one obtains that complete burning of 1 ml of 100 % ethanol (volume measured at 25°C) produces 764 ml (STPD) CO\textsubscript{2} and consumes 1146 ml (STPD) O\textsubscript{2}. The practical problem is the construction of a burner which ensures complete combustion.

The only way to avoid uncontrolled evaporative losses of alcohol during burning is to use a burner without a wick. Burning can be performed in an open vessel and if the area of the liquid surface as well as the vessel material are optimally selected, results with very good reproducibility are obtained. As a rough guide we can recommend a cylindrical ceramic or glass vessel with a height of some 20 mm and a diameter of 30 mm for burning 5 ml of alcohol.
13.2.5 Flow calibration and validation

In addition to the general problems associated with flow measurements described in Chapter 9, the calibration of flow sensors also causes difficulty. A common primary method is to conduct a set of steady flows through the flow sensor to a volumetric gasmeter, and define the flow by measuring the collection time. A gas bell can also be used as the gas supply, by emptying a full bell at constant rate using appropriate weights.

Even if the flow sensor has been calibrated for specific gases and conditions with steady flows, it will not necessarily ensure correct results in highly dynamic situations encountered when measuring mechanical ventilation.

Instead of direct flow calibration, the only practical routine method is volume calibration by pumping with a syringe of a fixed volume. With this method, some of the dynamic effects can be taken into account. In some more sophisticated devices the software may follow the pumping rate and accept the calibration only when pumped within the relevant flow range.

When the dilution method is used, flow calibration in the ordinary sense is not needed. The flow generated by the flow generator can be measured and its long term stability checked in an indirect way by using the gas infusions or quantitative alcohol burning, as described above.

13.2.6 General problems of validation

The main need for independent validation of the whole system is the fact that even if the gas sensors and flow sensor are calibrated individually, considerable error may exist in the final results. A systematic difference may occur in the gas results between calibration and measurement if the flow and pressure conditions inside the sampling tubing circuitry are not carefully designed to be equal between these two situations. Similar problems may also be involved in flow calibration.

The general, in vitro validation philosophy is a difficult issue since, as seen above, special, high-quality technical equipment with very careful use is needed and there are very few hospitals which have the resources for this. The RQ check with alcohol burning with room air is often the only method which can be routinely performed reliably with simple equipment. A kit for alcohol burning on a quantitative basis, as described in Section 13.2.4 is available at least from one manufacturer of gas exchange monitors (Datex-Ohmeda).
The other alternative to validate the overall performance of the system is through in-vivo measurements. Either results can be compared with standard predicted values with proper patients, or then with results from another monitor whose function is known to have been validated.
14 CLINICAL APPLICATIONS

14.1 Canopy measurements

A canopy is an enclosure designed to completely cover the patient’s head, allowing collection of respiratory gases. A flow of air is arranged through the canopy to ensure that inspired CO$_2$ level remains at an acceptable level. The classical canopy constructed by Kinney /51/ is a cubic, rigid, transparent plastic box with a neck seal and a balanced 40 L/min inflow and outflow of air. The O$_2$ and CO$_2$ concentrations of the outflow are sampled to allow calculation of $v_{O2}$ and $v_{CO2}$. It is also possible to connect a spirometer to this system for precise measurement of respiration.

An alternative light-weight, semi-closed canopy design has been realized by Datex-Ohmeda /48/. This canopy with a basic geometry of a half ellipsoid is formed out of 1 mm thick, transparent polycarbonate. It is provided with a wide edge of soft plastic cloth which seals the canopy adequately when wrapped under the head and around the neck of the patient. The effective volume of the canopy, when the patient’s head is inside, is about 15 liters which, together with its aerodynamically favourable form, means that rebreathing of CO$_2$ is smaller than with a Kinney type of canopy.

Another simplification is that only the outflow from the canopy is kept constant with the flow generator, which means that the inflow varies with breathing of the patient. Then, if the expiration flow exceeds the outflow, the flow direction in the inflow is reversed and some expiration gas may instantaneously be lost unless reserve volume is available in the inflow tubing.

Almost all canopy measurements have been made with only room air. With a Kinney-type absolutely leakage free construction, use of elevated F$_{IO2}$ levels is in principle possible, but even then availability of a F$_{IO2}$ source stable enough may become a problem. The fluctuation of F$_{IO2}$ should be minimal because the O$_2$ difference to be measured is only 0.5...1 %.

Selection of the optimum flow is always a compromise between signal level and the inspired CO$_2$ concentration. For normal adults at rest, 40 L/min is a good compromise; but for children it is too much, and for adults of large size or under exercise it is too little. An important aspect to be noted if the flow rate is changed is that resolution of the final results depends always on the resolution of the CO$_2$ and O$_2$ measurement. This means that if the flow is adjusted to allow a light exercise test for canopy subject, then the normal rest values of $v_{O2}$ and $v_{CO2}$ in the beginning of the test suffer in accuracy because very small concentrations have to be measured.
14.2 Canopy leaks

In a configuration where air is sucked through a canopy by a flow generator, a small under-pressure is present inside the canopy. So, if small leaks exist due to inadequate sealing of the canopy, the total input flow is simply distributed between the main inlet and the leaks. In the case that the expiratory flow instantaneously exceeds the total flow, the flow direction will also be reversed in the leaks and some minor amounts of CO₂ produced by the subject will be lost. This effect is smaller with an aerodynamically designed canopy than with a mixing chamber type. It can be shown that even if some expired gas is lost it will never effect the RQ as long as room air is used.

In conclusion, the effect of leaks when moderate attention is paid to sealing is negligible. Based on these facts, even half-open hoods have been proved to work satisfactorily /52/. 
15 MEASUREMENTS DURING MECHANICAL VENTILATION

15.1 Effects of $F_{\text{I}O_2}$ fluctuations

Many problems are involved with the accurate measurement of $O_2$ consumption during mechanical ventilation with enriched levels of $F_{\text{I}O_2}$. The ultimate need for precise measurement of $(F_{\text{I}O_2} - F_{\text{EO}2})$ differences at high $O_2$ has already been discussed, but an additional difficulty is involved with the stability of the $F_{\text{I}O_2}$ level delivered to the patient. The air/oxygen blenders of ventilators have, by no means, been designed to meet the stability requirements of gas exchange monitors. The effect of unstable $F_{\text{I}O_2}$ and the quality of some blenders have been discussed in the literature /53/, but clear guidelines of what is an acceptable level of $F_{\text{I}O_2}$ stability from a practical point of view have, to our knowledge, not been given.

When using the breath-by-breath method, $F_{\text{I}O_2}$ stability is not a problem in principle since the instantaneous $F_{\text{I}O_2}$ fractions are followed and used in calculations. But, in practice, this is not quite certain, because $F_{\text{I}O_2}$ fluctuations tend to be related to pressure, which means that the reliability of the final results still depends on the tolerance of the $O_2$ sensor to pressure or, on the quality of the pressure compensation.

In normal, open systems with a mixing chamber, the relevant $F_{\text{I}O_2}$ value following from the definition of $v_{\text{I}O_2}$ (Equation 28) is the flow weighted average $F_{\text{I}O_2}$. An error may arise in the common situation where the normal average of $F_{\text{I}O_2}$ over several breath cycles is used. Since the flow in volume controlled ventilators is more or less constant during the inspiratory cycle, it would be enough to arrange sampling in phase with the breath cycle, so that $F_{\text{I}O_2}$ values during expiratory phase are excluded from the average. Phased sampling is technically possible in principle, but practical reasons, like transport delays of gas sampling, make it an unappealing solution.

From a practical point of view, the key aspects concerning $F_{\text{I}O_2}$ stability are:

1. What is the maximum fluctuation of $F_{\text{I}O_2}$ that can be allowed and how to check it.

2. How to improve $F_{\text{I}O_2}$ stability, if it is necessary.

An unstable $F_{\text{I}O_2}$ will naturally be reflected as greater than normal fluctuation in oxygen consumption results. Depending on the patient status and measurement algorithms, quite large minute-by-minute fluctuations may be possible even in situations where $F_{\text{I}O_2}$ is stable. This means that the only way to
check the contribution of poor $F_{I(O_2)}$ quality to the final results is
to run a validation test according to Section 13.2.3. for the
ventilator and blender combination in question. The $v_{O_2}$
baseline test, by ventilating a test lung alone, is the most
convenient check. Unstable $F_{I(O_2)}$ will result in a nonzero
fluctuating $v_{O_2}$. On the other hand, pure pressure effects of $O_2$
sensor may also lead to similar errors and it may sometimes be
difficult to separate these two factors. As a rough rule, one can
say that if $v_{O_2}$ (or $F_{I(O_2)} - F_{E(O_2)}$ difference) as averaged over a
clinically relevant period (e.g., 15 minutes) still shows either a
considerable fluctuation or gives a permanent steady baseline,
one should make an attempt to improve $F_{I(O_2)}$ stability.

A quite common reason for poor $F_{I(O_2)}$ quality is the sensitivity of
the air/oxygen blenders to pressure delivered by the
compressed air source. In an ordinary compressed air network,
pressure drifts continuously downwards until the central
compressor pumps it up again. In this case, an additional
pressure regulator between the compressed air source and
blender helps considerably.

Another powerful method is /53/ to add an external blender
and divide its output to both inputs of the ventilator's own
blender. And, finally, the ultimate possibility is to run the
ventilator from a gas cylinder with a constant $O_2$ concentration.
This test would at least reveal if the origin of fluctuations is $F_{I(O_2)}$
instability or pressure effects.

Instead of baseline simulation, a normal RQ or gas infusion
simulation can be run with the system if $F_{I(O_2)}$ difficulties are
suspected. From the results of steady state alcohol burning or
infusion one has to judge if the fluctuations observed are so
great that they will interfere with the interpretation of results in
patient measurements.

15.2 Airway pressure effects

As described in Chapter 12, the pressure effects associated with
mechanical ventilator may introduce major errors to the $O_2$
measurement. Either the $O_2$ sensor has to be inherently pressure
insensitive or the pressure effect has to be compensated,
requiring pressure measurement in the sampling circuit. In
general, a pressure related to the mean airway pressure is
relevant in compensation. The pressure effect is naturally most
dominant if PEEP (positive end expiratory pressure) is applied.
During PEEP, the peak pressure actually increases more than the
amount of PEEP. The true pressure effect can be checked with
normal validation methods. Gas infusion simulation results
should not be changed significantly if PEEP is changed. This test
has to be made carefully, since it may happen that PEEP
also changes $F_{IO2}$ and nitrogen simulation Equation (32) is quite sensitive to $F_{IO2}$. In other words, any change in $\nu_O2$ during $N_2$ simulation can be either due to $O_2$ pressure effect or change in $F_{IO2}$ level because of PEEP effect to the gas blender. Alcohol burning is a better test for this purpose.

### 15.3 Continuous flow ventilators

Ventilators using continuous flow pneumatic techniques are very problematic in metabolic measurements. The high flow dilutes the gas concentrations down to a level almost as low as with canopy measurements. Then, the stability requirement for $F_{IO2}$ becomes extremely high. Since the performance of air/oxygen blenders at high flows is usually inferior to that at low flows of demand valve intermittent flow systems, it is quite unrealistic to try to achieve reasonable gas exchange results with these type of ventilators unless the inspiratory gas is taken from a gas tank, or the expiratory gases separated from the main stream flow /56/.

### 15.4 Leak detection

Leaks in the tubings and connectors of the ventilator set-up or in the internal tubings of the monitor easily generate errors, especially in $\nu_O2$. At high $F_{IO2}$, air leaking into the gas circuit dilutes $O_2$ concentration and changes the $O_2$ difference. On the other hand, there is practically always an over-pressure in the inspiratory side of the ventilator and leaks inwards are not possible. In the expiratory side an outside leak also can produce error since some expiratory $CO_2$ is lost.

Leaks can often be revealed by visual inspection with help of air bubbles from liquid leak detector. Ventilation of a test lung alone may reveal a leak if significant $O_2$ consumption results.

A leak around the endotracheal tube always makes gas exchange measurements impossible, since an unpredictable amount of expiratory gas is lost.
A normal open system has a time constant depending on the volume of mixing chamber and minute ventilation. We can simply write:

\[ t = \frac{V}{v_E} \]  

(44)

where \( v_E \) is the minute ventilation and \( V \) the total effective volume of the system.

The measurement system can be removed from the steady state by changing either \( F_{O_2} \) or minute ventilation. The dynamic transfer function of the system will result in a step change in \( O_2 \) consumption, which then returns to steady state with time constant \( t \). Figures 19a-d give a schematic illustration of the response of \( O_2 \) consumption when \( F_{O_2} \) or \( v_E \) are changed stepwise.

\( CO_2 \) production should not react when \( F_{O_2} \) is changed, except for possible true changes in patient \( CO_2 \) output. The response to \( v_E \) change is similar to that with \( v_{O_2} \) from the measurement system point of view. However, note again that \( v_E \) change will induce a non-steady state in the \( CO_2 \) pools of the body which may last 1 hour or so /30/.

How the step response is observed in results naturally depends on the algorithms used and the interval between displaying results but it is clear that a certain period after a step change of ventilator setting has to be excluded as clinically irrelevant data. With fast-response sensors, and by following changes of gas signals, algorithms can be developed to detect automatically these special situations, label them as artifacts and neglect this data from the final results. The change of \( O_2 \) difference is clearly the most sensitive criterion to detect \( F_{O_2} \) change, but changes in \( CO_2 \) production, are also useful, especially to reveal disconnection of the patient from the ventilator e.g., because of suction. The artifact algorithms usually also include extra time, e.g., 5 to 10 minutes after the artifact is already over according to the basic criteria, to ensure a new steady state.

On the other hand, a very sensitive artifact algorithm may lead to a situation where no results from a restless and unstable patient are accepted.
Figure 19a Effect of upwards step change of $F_{102}$ upon $v_{O2}$

Figure 19b Effect of downwards step change of $F_{102}$ upon $v_{O2}$

Figure 19c Effect of upwards step change of $v_E$ upon $v_{O2}$

Figure 19d Effect of downwards step change of $v_E$ upon $v_{O2}$
16 OVERALL ACCURACY

The error sensitivity of the Haldane transformation algorithm has been studied in a detailed mathematical approach by Ultmann and Bursztein /54/. Later, Burema and Teirlinck /55/ have presented analysis with detailed relevant numeric examples. Here we simplify the approach, aiming to be able to give practical rules of thumb to evaluate error accumulation at different $F_{O2}$ levels.

We start from basic formulas:

\[ v_{CO2} = F_{ECO2} \cdot v_E \] (45)

\[ v_{O2} = \frac{v_E}{1 - F_{IO2}} \cdot [(F_{IO2} - F_{EO2}) - F_{IO2}F_{ECO2}] \] (46)

For simplification of the error analysis, it is more convenient to deal with relative errors than absolute ones. When looking at functions like (45) and (46) which are products of several measured variables, the relative error of the final result in the worst case is the sum of the relative errors of the variables.

The error of flow measurement contributes in a straightforward manner to the final error. Effect of gas measurement errors can also easily be seen in $v_{CO2}$ but in $v_{O2}$ the errors interact in a more complicated way.

The relative error approach is very simple in cases where the main error source is gain drift. This is often the situation in practice, since the baseline errors can automatically be compensated for during the measurement. Gain drifts can be estimated in connection of calibrations. For $v_{CO2}$, the relative error is simply the sum of the relative errors of CO$_2$ measurement and flow measurement. For example, a drift of CO$_2$ between calibrations from 4.0 % to 4.1 % is a relative error of 2.5 %, which, when added to the drift of flow sensor gives an estimation for the total error in worst case, i.e. when both CO$_2$ and flow have been drifting to the same direction. It has to be emphasized again that a systematic deviation may exist between calibration and measurement situation, and the only way to eliminate this is to check the final $v_{CO2}$ results with $v_{CO2}$ simulation. If any systematic baseline error exists, it means that the total relative error is greater and will become dependent on the level of results so that with small values of variables the relative error increases.
According to Equation (46) for $v_{O_2}$, one can see that the effect of $v_E$ is straightforward, but for analysis of gas errors one has to determine the contribution of oxygen difference ($F_{I_{O_2}} - F_{E_{O_2}}$), absolute $F_{I_{O_2}}$ and also $F_{E_{CO_2}}$. At first glance, it may be surprising that errors of CO$_2$ measurement also affect O$_2$ consumption, but this follows simply from the basic assumption of the Haldane transformation. One can see that this interaction becomes very strong at high $F_{I_{O_2}}$ levels when both terms to be subtracted within the brackets of Equation (45) become almost equal. The worst case situation is obviously when CO$_2$ and O$_2$ drift to opposite directions. If the errors are in the same direction they almost cancel one another.

Formulation of Equation (46) emphasizing the oxygen difference is intended to reveal that error of oxygen difference is dominating compared to $F_{I_{O_2}}$ error. Detailed error sensitivities for all the variables have been calculated in Appendix B, but as a rough rule we can say that if on $F_{I_{O_2}}$ level of 60% the same relative error is assumed for oxygen difference and for the absolute $F_{I_{O_2}}$, the effect of the $F_{I_{O_2}}$ error is ten times smaller. This makes the use of direct differential O$_2$ measurement clearly more attractive than the separate measurement of $F_{I_{O_2}}$ and $F_{E_{O_2}}$.

In conclusion the simple rules of thumb for the worst case error estimation of gas exchange parameters when Haldane transformation is used are as follows:

* **CO$_2$ production:** Add relative errors of CO$_2$ and flow measurement.

* **O$_2$ consumption:** Add relative errors of O$_2$ measurement multiplied by a factor $1/(1-F_{I_{O_2}})$, relative error of CO$_2$ measurement multiplied by a factor $F_{I_{O_2}}/(1-F_{I_{O_2}})$ and relative error of the flow measurement.

* **RQ:** Add relative errors of O$_2$ and CO$_2$ measurements multiplied by $1/(1-F_{I_{O_2}})$. 
A GENERALIZED PERFORMANCE CHARACTERISTICS OF THE SENSORS

Whenever physical quantities are measured and the performance of a sensor or an instrument is evaluated, the first question often is: how accurate is it? However, anyone familiar with the theoretical basics of measurement technology knows that it is impossible, and wrong, to answer this question with a single number, say e.g., ±5 %. The purpose of this text is to give an introduction to precise terminology of the measurement technique.

A sensor or a transducer is a device converting an input physical quantity to an output signal which usually is an electrical voltage or current. In addition to the desired input every instrument has a number of undesirable interfering inputs. Effects like temperature, humidity and atmospheric pressure are the most obvious ones, but several others, depending on the type of the measurement, are possible.

The law between the output and the input of the sensor is called a characteristic curve and it is obtained with a process called calibration. In applications where measured quantities are constant or vary only quite slowly we can speak about the static performance characteristics, which respectively is obtained through static calibration. In cases where quantities are varying rapidly, the dynamic relations between input and output has to be examined. Instead of dynamical calibration which is usually difficult, the dynamic characteristics are obtained by using theoretical models involving differential equations.

In general, static calibration refers to a situation where all inputs except the desired one are kept constant. The input under study is then varied over some range of constant values, causing output to cover some range of values. The characteristic curve obtained in this way will give input-output relation to any other value under the stated constant conditions of all other inputs. The curve can be a straight line when we have a linear characteristic curve. In the opposite case it is nonlinear.

Linearity can be defined in several ways. It describes the amount of deviation of the characteristic curve from the straight line. It has to be noted that nonlinearity as such does not make the sensor more inaccurate if a linearization is done according to a well known characteristic curve. Maximum deviation from the straight line can be expressed as a per cent of actual reading or of full scale. The most realistic way to specify nonlinearity is combination of both:
Nonlinearity $= \pm A \%$ of reading or $\pm B \%$ of full scale, whichever is greater.

This definition takes into account the fact that it is impossible to measure small relative deviations at the low end close to the zero of the characteristic curve. The overall tolerance band according to this definition is illustrated in Figure 1A.

![Diagram of nonlinearity](image)

**Figure 1A** The overall tolerance band for a characteristic curve according to definition of nonlinearity

**Sensitivity** of the sensor is defined as a ratio between change of output quantity and change of input quantity. Sensitivity is constant for whole range for a linear device but depends on the input level for a nonlinear device. Sensitivity factor is quite often called **gain**.

The output for zero input is called **bias**. In an ideal case the bias should be zero. Both sensitivity and bias usually drift with time (see Figure 2A) and with changing ambient conditions a new calibration and readjustment of sensitivity and bias factors are needed after certain intervals to maintain the specified performance. The normal routine calibration should be of two point type which makes both bias and sensitivity check possible. If bias drift can be taken as negligible, one-point calibration with sensitivity readjustment is enough.
Resolution is the smallest change of the input quantity which gives a measurable change of output.

Threshold is the smallest measurable absolute input i.e. how much the input has to be increased from zero before a measurable output can be detected. A device with high sensitivity does not automatically have a good resolution and small threshold.

Accuracy describes the deviation of the obtained measurement result from the “true” value. The reference method for the true value should be traceable to a “gold standard”. The reference method should be preferably more accurate, by a factor of 10 or more, than the system to be studied, to obtain a meaningful estimate of accuracy.

The total error is the combination of random error and systematic error. Random error is statistically distributed and can be in an ideal case of Gaussian type, specified by terms of the average and standard deviation. Random error is usually closely connected to noise level of signal. Precision and repeatability (or reproducibility) are terms also used to describe the amount of the random error of the system.

The systematic error component comes from drifts of sensitivity and bias but can be present also immediately after
calibration if it is not possible to perform calibration in exactly the same configuration as the measurement is done.

When combination of component errors in overall system accuracy is discussed (see Appendix B) the most difficult question is how to assess the contribution of drifts of the various sensors. In practice, it is often unrealistic to try to find out if the drifts are randomly distributed or systematic. The worst case approach is the only possibility, even if it gives a somewhat misleading impression of the most probable accuracy of the system.

To summarize, instead of giving or asking a single number describing accuracy of an instrument or a measuring system, one should discuss the following points:

1. What are the predicted errors of baseline or zero and sensitivity immediately after calibration.

2. What is the repeatability (random error) at a relevant signal level.

3. What is the required calibration interval. What is the calibration method and its accuracy.

4. What are the predicted errors just before recalibration.

One always has to be sceptical when accuracies of the order of or better than ±1 % are promised for any measurement system. It is very seldom that even the “gold standard” with this accuracy is easily available.

In many practical applications, including clinical ones, a moderate systematic error can be tolerated if the repeatability is good.
B  DETAILED ERROR ANALYSIS

Expanding a function \( f(u_1, u_2, u_3, u_4) \) in a Taylor series and neglecting terms of second and higher orders, we get

\[
df = f(u_1 + Du_1, u_2 + Du_2, u_3 + Du_3, u_4 + Du_4) - f(u_1, u_2, u_3, u_4)
\]

\[
df = \frac{df}{du_1} + \frac{df}{du_2} + \frac{df}{du_3} + \frac{df}{du_4} \quad \text{(B1)}
\]

In the following we apply this to the formulas of \( v_{O_2}, v_{CO_2} \) and RQ.

1B  \( O_2 \) consumption

Using Haldane transformation we have

\[
v_{O_2} = \frac{V_E}{1 - F_{IO_2}} \times \left( (F_{IO_2} - F_{EO_2}) \cdot F_{IO_2}F_{ECO_2} \right) \quad \text{(B2)}
\]

Let

\[
F_{IO_2} - F_{EO_2} = F_{DO_2} \quad \text{(B3)}
\]

and

\[
\frac{F_{ECO_2}}{F_{DO_2}} = r \quad \text{(B4)}
\]

Then (B2) can be rewritten as

\[
v_{O_2} = F_{DO_2} \cdot V_E \cdot \frac{1 - rF_{IO_2}}{1 - F_{IO_2}} \quad \text{(B5)}
\]
We can see that $v_{O2} = f (F_{IO2}, F_{DO2}, F_{EO2}, v_E)$. Then according to (B1):

\[ d v_{O2} = D F_{IO2} \frac{d v_{O2}}{d F_{IO2}} + D F_{DO2} \frac{d v_{O2}}{d F_{DO2}} + D F_{ECO2} \frac{d v_{O2}}{d F_{ECO2}} + \frac{d v_E}{d v_E} \]

(B6)

By partial differentiation we get from (B2) or (B5)

\[ \frac{d v_{O2}}{d F_{DO2}} = D O_2 \cdot v_E \cdot \frac{1 - r}{(1 - F_{IO2})^2} \]

(B7)

\[ \frac{d v_{O2}}{d F_{ECO2}} = \frac{F_{IO2}}{1 - F_{IO2}} \]

\[ \frac{d v_{O2}}{d v_E} = \frac{1 - r F_{IO2}}{1 - F_{IO2}} \]
The relative error of \( v_{o2} \) is obtained by dividing both sides of (B6) by \( v_{o2} \). Then using (B7...B10) we get

\[
\frac{d_v}{v_{o2}} = \frac{F_{iO2}(1-r)}{(1-F_{iO2})(1-rF_{iO2})} + \frac{1}{1-rF_{iO2}} + \frac{DF_{DO2}}{F_{DO2}}
\]

\[
- \frac{rF_{iO2}}{1-rF_{iO2}} \frac{DF_{ECO2}}{F_{ECO2}} + \frac{DV_E}{V_E}
\]  

(B11)

This equation shows directly how much relative errors of the different variables contribute to the final relative error. The coefficients of the terms of (B11) can also be called error sensitivity factors. Since \( r \) is closely related to RQ and is of the order of unity, one can see immediately that the error sensitivity factor of \( F_{DO2} \) is the highest one and increases rapidly with increasing \( F_{iO2} \).

2B CO\(_2\) production

We start from equation

\[
v_{CO2} = F_{ECO2} \cdot V_E
\]  

(B12)

The differentiation is trivial in this case and the final result is simply

\[
\frac{d_v}{v_{CO2}} = \frac{DV_E}{V_E} + \frac{DF_{ECO2}}{F_{ECO2}}
\]  

(B13)

The error sensitivity factor is one for \( V_E \) and \( F_{ECO2} \) and zero for the other variables.
3B  Respiratory quotient

By using (B12) together with (B2...B4) we get according to the definition of RQ:

\[ RQ = \frac{v_{CO2}}{v_{O2}} = \frac{1 - F_{IO2}}{r^{-1} - F_{IO2}} \]  \hspace{1cm} (B14)

Differentiation results to

\[ \frac{\text{d}RQ}{RQ} = \frac{(1 - r) F_{IO2}}{(1 - rF_{IO2})(1 - F_{IO2})} \frac{\text{d}F_{IO2}}{F_{IO2}} + \frac{1}{1 - rF_{IO2}} \frac{\text{d}F_{DO2}}{F_{DO2}} \]

\[ \cdot \frac{1}{1 - rF_{IO2}} \frac{\text{d}F_{ECO2}}{F_{ECO2}} \]  \hspace{1cm} (B15)

4B  Worst case errors

As can be seen from (B11), (B13) and (B15), the error sensitivity factors can be positive or negative. The same is true for the relative errors of the variables. The absolute values for the worst case error of our variables \(v_{O2}, v_{CO2}\) and RQ can be calculated from table B1, which is combination of (B11), (B13) and (B15). Here E is the relative error of the variable in question.
Table B1  Error sensitivity factors for $v_{O2}$, $v_{CO2}$ and RQ

<table>
<thead>
<tr>
<th></th>
<th>$EF_{IO2}$</th>
<th>$EF_{DO2}$</th>
<th>$EF_{ECO2}$</th>
<th>$E_{v_{E}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{vO2}$</td>
<td>$\frac{F_{IO2}(1 - r)}{(1 - F_{IO2})(1 - rF_{IO2})}$</td>
<td>1</td>
<td>$rF_{IO2}$</td>
<td>1</td>
</tr>
<tr>
<td>$E_{vCO2}$</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ERQ</td>
<td>$\frac{F_{IO2}(1 - r)}{(1 - F_{IO2})(1 - rF_{IO2})}$</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Numerical example 1.** Assume $F_{IO2} = 50\%$, RQ = $r = 1$ and relative errors of $F_{IO2}$, $F_{DO2}$, $F_{ECO2}$ and $v_{E}$ to be $\pm 1\%$ each. Then the relative errors for the worst case are

$E_{vO2} = 0 + 2 + 1 + 1 = \pm 4\%$

$E_{vCO2} = 0 + 0 + 1 + 1 = \pm 2\%$

$ERQ = 0 + 2 + 2 + 0 = \pm 4\%$

**Numerical example 2.** Same as example 1, but $r = 0.9$ (RQ = 0.82)

$E_{vO2} = 0.18 + 1.82 + 0.82 + 1 = \pm 3.82\%$

$E_{vCO2} = 0 + 0 + 1 + 1 = \pm 2\%$

$ERQ = 0.18 + 1.82 + 1.82 + 0 = \pm 3.82\%$
LIST OF REFERENCES


54. Ultman JS, Burszteins S: Analysis of error in the determination of respiratory gas exchange at varying F_{IO2}. J. Appl. Physiol. 50: 210-216, 1981.