ARTERIAL BLOOD GAS TENSIONS AND pH

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- 1 The definition of P_{O_2} and its relationship to the oxygen saturation (S_{O_2}) by the oxygen dissociation curve (ODC) is described with details of the ligands of the ODC and the effects of haemoglobinopathies on P_{50} (the position of the ODC) and the slope of the ODC (Hill's 'n').
- 2 The definition of P_{CO_2} and description of CO_2 transport by blood leads to consideration of the basis of acid base balance.
- 3 Acid base balance is expressed in terms of arterial blood (H^+) (or pH) P_{CO_2} relationship using a non-logarithmic diagram.
- 4 The measurement of arterial blood gas tensions is described with comments on arterial puncture and available modern automated blood gas electrodes and their calibration.
- 5 Non-invasive indirect measurements of blood gas tensions, by ear oximetry are described, with calibration figures on the Hewlett-Packard 47021A ear oximeter. End-tidal P_{O_2} and P_{CO_2} measurements by mass spectrometer or infra-red CO_2 analyser, and of transcutaneous P_{O_2} measurements by a heated polarographic electrode are described.
- 6 These measurements are necessary to study the effects of pharmacological agents on the chemical control of breathing, on pulmonary gas exchange, and on acid base balance in humans. The measurements are in everyday use in clinical practice, both to aid diagnosis of respiratory diseases, assess their severity, and to quantitate the effects of therapeutic agents.

The major respiratory function of the lungs is to add oxygen to the blood and to remove CO_2 . Thus the measurement of concentration of these gases in the arterial blood leaving the lungs, when coupled with knowledge of the inspired oxygen concentration, allows an accurate assessment of the gas-exchanging function of the lungs. When breathing air the inspired oxygen concentration $P_{I_{O_2}}$ is 20.94% and the inspired CO_2 concentration 0.03%

$$P_{I_{O_2}} = (P_B - 47) \times F_{I_{O_2}} \quad (1)$$

where P_B is barometric pressure; 47 mmHg, saturated vapour pressure of water at 37°C; $F_{I_{O_2}}$, inspired oxygen concentration.

Equation (1) yields an inspired partial pressure at sea level of

$$20.94\% \times 100 \text{ kPa} = 20.9 \text{ kPa};$$

or

$$20.94\% \times (760 - 47) = 147 \text{ mmHg}.$$

This partial pressure (P_{O_2}) is a direct measurement of the molecular concentration of free oxygen in the gas phase. A similar concept of partial pressure (or tension) can be applied to a gas in solution, where, again, this measurement is directly proportional to the molecular concentration of the free gas in

solution. In the case of oxygen this tension (P_{O_2}) is related to the total concentration of oxygen in blood (C_{O_2}) by the sigmoidal oxygen dissociation curve (ODC). This depends upon the chemical properties of haemoglobin, and on the concentration of other ligands which combine with haemoglobin and thus affect oxygen binding. The oxygen saturation (S_{O_2}) which determines the colour of the blood, and thus can be measured spectrophotometrically, is defined as:

$$S_{O_2} = \frac{\text{oxygen concentration in that blood sample}}{\text{oxygen concentration of that blood when fully saturated}}$$

The denominator of this equation, the oxygen concentration when fully saturated, is also known as the oxygen capacity which in turn depends on the haemoglobin concentration in the blood sample, for each gram of haemoglobin can combine with 1.34 ml of oxygen at 37°C. Thus in anaemia, where there is a low haemoglobin concentration, the oxygen saturation (S_{O_2}) may be the same as that in a patient with polycythaemia, but the oxygen concentration of the blood would be much less in the anaemic patient.

Oxygen dissociation curve (Garby & Meldon, 1977)

The shape and position of the ODC depends on temperature and the concentration within the red cells of other ligands of haemoglobin which may also bind to this molecule, in addition to oxygen. The position of the ODC is defined by the P_{O_2} at 50% saturation (Figure 1), known as the P_{50} , and the slope of the curve by Hill's 'n' in the logarithmic equation:

$$\log \left(\frac{S_{O_2}}{1 - S_{O_2}} \right) = n \log P_{O_2} \quad (2)$$

This equation effectively linearises the sigmoidal ODC over the majority of its range. Both P_{50} and 'n' are dependent on the amino acid sequence in the two chains of the globin molecule. They are thus abnormal in the inherited haemoglobinopathies where genetic abnormalities in haemoglobin synthesis with a change in amino acid sequence affects both P_{50} and 'n'. Over 190 such variants are now known, stable genetic mutants with low P_{50} including haemoglobin Bethesda, Brigham, Chesapeake, Hiroshima, Kansas, Little Rock and Yahama. Thus, for example, haemoglobin Chesapeake has a P_{50} of 2.5 kPa (as opposed to the normal value of 3.4 kPa at the usual pH 7.4) and a value of 'n' of 1.4, compared to the normal 'n' value of 2.6–3.0 for normal adult haemoglobin. In practice this haemoglobinopathy is associated with polycythaemia.

Oxygenation of the haemoglobin molecule releases hydrogen ions, or protons, so that by this *Bohr effect*

oxygenated haemoglobin appears to be a stronger acid, or proton donor than does reduced haemoglobin. This Bohr effect is defined as:

$$\text{Bohr effect} = \frac{\Delta P_{50}}{\Delta \text{pH}}$$

The Bohr effect is normally 0.5 and reflects the importance of the link between oxygen and CO_2 transport within the red cell. The Bohr effect is so important that the P_{50} is always corrected to a plasma pH of 7.4 (although the pH within the red cell (pHi) is then 7.18 or thereabouts). In addition to the pH effect, haemoglobin also combines physiologically with CO_2 to form carbamino-haemoglobin, but again this depends upon the oxygenation status of the haemoglobin molecule. This oxy-labile CO_2 transport (the Christiansen–Douglas–Haldane effect) depends on the terminal valine residues in the beta chains of the haemoglobin molecule. Oxygenation of the haemoglobin molecule displaces CO_2 , so that the P_{CO_2} of a closed blood sample will rise as the S_{O_2} rises.

Other ligands of the haemoglobin molecule include 2-3-diphospho-glycerate (2-3, DPG), a by-product within the Embden–Meyerhof glycolytic pathway in the red cell. DPG is present in almost equimolar concentrations to haemoglobin in the red cell, and an increase in DPG lowers the P_{50} . The enzyme systems affected both in synthesis and degradation of DPG are very pH dependent, and it now seems that the pH within the red cell is the most important determinant of DPG levels. Transfused blood stored in acid-citrate dextrose contains little DPG, and a massive transfusion of bank blood may thus interfere with oxygen transport by lowering P_{50} for several hours or even days.

Other less physiological ligands affecting P_{50} include carbon monoxide (CO), which is produced both from endogenous haemolysis and as a result of heavy cigarette smoking. Values of up to 20% carboxyhaemoglobin are not uncommon at the end of a heavy smoker's day. Methaemoglobin, where the Fe ion is present in the oxidized Fe^{+++} form cannot combine reversibly with oxygen, and thus does not function as a respiratory pigment. Sulphaemoglobin has similar properties to methaemoglobin in this regard, and these two abnormal pigments can be identified spectrophotometrically in a blood sample.

Figure 1 The oxygen dissociation curve relating blood oxygen saturation (S_{aO_2}) to oxygen tension (P_{aO_2}), at three different levels of hydrogen ion activity (H^+). Inset is a plot of Hill's equation (see text). The P_{50} (7.4) is the P_{O_2} at 50% saturation, when $\text{pH} = 7.40$ ($[\text{H}^+] 40 \text{ nmol/l}$) (from Flenley, 1978).

Carbon dioxide transport

Carbon dioxide, which is of course a major product of metabolism, is carried as carbamino-haemoglobin in the blood as described above. However, the major form of CO_2 in a blood sample is as bicarbonate ion (HCO_3^-) in the plasma, although some HCO_3^- is also present in the red cell. The equation:

can be used to describe the basis of acid base balance in the body. The P_{CO_2} , or partial pressure of CO_2 of arterial blood, depends largely on pulmonary gas exchange, but due to the small arterio-venous difference in P_{CO_2} , and to the linear form of the CO_2 dissociation curve in the physiological range the arterial P_{CO_2} is much less influenced by ventilation-perfusion imbalance within the lungs than is the arterial P_{O_2} . Thus measurement of the arterial P_{CO_2} reflects the level of alveolar ventilation; a departure from the normal range of 5.0 to 5.6 kPa (38–42 mmHg) in a resting subject breathing air almost invariably indicating either hyperventilation (with a low P_{CO_2}) or hypoventilation (with a high P_{CO_2}). As the lungs do not secrete oxygen it follows that such an elevated P_{CO_2} , in a patient breathing air at sea level, must be associated with a lowering of arterial P_{O_2} . This latter concept can be expressed more precisely in the approximate form of the alveolar air equation:

$$P_{\text{AO}_2} = P_{\text{I O}_2} - \frac{P_{\text{a CO}_2}}{R} \quad (4)$$

where $P_{\text{I O}_2}$ is the inspired oxygen tension: $P_{\text{a CO}_2}$ is the arterial CO_2 tension, and R is the gas exchange ratio (CO_2 output/ O_2 intake) which can safely be assumed to be 1.0–0.8 in a subject at rest.

Acid-base balance (Flenley, 1971)

The acid base status of the body can be conveniently represented by application of the law of mass action to equation (3), yielding the mathematical relationship:

$$[\text{H}^+] = \frac{K'_1 \alpha P_{\text{CO}_2}}{[\text{HCO}_3^-]} \quad (\text{Flenley, 1971}) \quad (5)$$

where $[\text{H}^+]$ = arterial hydrogen ion activity; K'_1 , first dissociation constant of carbonic acid in plasma; α , solubility of CO_2 in plasma; and P_{CO_2} , arterial P_{CO_2} ; $[\text{HCO}_3^-]$, arterial (or venous) bicarbonate concentration. This equation indicates that there is a linear relationship between $[\text{H}^+]$ and P_{CO_2} , when both are plotted on non-logarithmic scales, and that lines of equal bicarbonate concentration radiate from the origin of such a graph (Figure 2). This acid-base diagram also indicates the 95% confidence limits of single clinical disturbances of acid base balance, as observed in the whole arterial blood *in vivo*. Thus in a metabolic acidosis disturbance $[\text{H}^+]$ is the primary variable altered, from either overproduction or from a failure to excrete acid normally, or excessive loss of bicarbonate from the body. Physiological adjustment

Figure 2 Acid-base diagram, relating (H^+) (or pH) to P_{CO_2} , with lines of equal (HCO_3^-) concentration radiating from the origin. The significance bands ($\equiv$), derived from observations of whole blood *in vivo*, of single disturbances of acid base balance in the adult human are shown (from Flenley, 1978). $\square$, Normal range.

to this disturbance depends upon alterations in P_{CO_2} , as a result of changes in ventilation resulting from the change in the $[\text{H}^+]$ stimulus. In contrast, in respiratory disturbances of acid base balance, the primary variable altered is $P_{\text{a CO}_2}$. Thus in alveolar hypoventilation, revealed by a raised arterial P_{CO_2} , if this occurs acutely there will be relatively little compensation, so that $[\text{H}^+]/P_{\text{CO}_2}$ relationships lie in the acute respiratory band on the diagram. However, if the elevation of arterial P_{CO_2} from underventilation of the lungs persists for several days, then reabsorption of bicarbonate occurs in the distal tubules of the kidney, so that the plasma bicarbonate is increased, with the result that acid base relationships in the arterial blood then lie within the chronic respiratory band on the diagram. In primary hyperventilation, classically seen in pneumonia, pulmonary oedema, bronchial asthma, pulmonary thromboembolism, etc., P_{CO_2} falls with resultant respiratory alkalosis. It must be realized that this diagram applies to measurements made in the whole arterial blood *in vivo*. Tonometry of blood *in vitro* with CO_2 outside the body will yield different acid base relationships, due to a failure of equilibration with other body stores of bicarbonate. These differences led to the 'Great Trans-Atlantic Acid-Base Debate' some years ago, but with the modern availability of direct measurements of arterial blood these differences are mainly of interest to the

physiological chemists, and have little direct relevance to clinical medicine.

Measurement of blood gas tensions

Arterial blood is obtained by direct puncture, usually of the left brachial artery in a right-handed person, after infiltrating 2–3 ml 1% xylocaine around the vessel. An all-glass, heavily siliconed heparinized syringe is used, containing a washer, so that the dead space of the syringe is entirely filled by the heparin solution. With an SWG 21 gauge needle an anaerobic sample of arterial blood is thus obtained. The only proof of successful arterial puncture is to observe blood pulsating into the syringe directly, as the colour of the blood by itself will never provide a reliable guide. Following puncture a gauze swab is firmly held in place over the puncture site for five minutes, by means of a tightly applied 3 in crepe bandage. Full details of the procedure are given by Flenley (1980). The anaerobic blood sample is then taken, still in the same syringe, directly to the blood gas electrode, within no more than five minutes of withdrawal from the patient.

Modern automated gas electrodes (Table 1) provide accurate measurements of pH ($\text{pH} = \log 1/[\text{H}^+]$), P_{O_2} and P_{CO_2} , and the derived variables. The accuracy of these measurements depends entirely on the calibration procedure for the electrodes. Traditionally, calibration has been carried out by bubbling water-saturated gases of known composition through the electrode chambers, the P_{O_2} and P_{CO_2} of these mixtures being known from independent analysis (usually by chemical means using the Lloyd–Haldane apparatus, and knowledge of the prevailing barometric pressure). However, different values of P_{O_2} and P_{CO_2} are registered by the blood gas electrodes with such gas mixtures, when compared to the readings on blood or solutions which have been equilibrated by tonometry with these gas mixtures. This difference is particularly important in the case of P_{O_2} measurements, and other methods of quality control for blood gas tension measurements have therefore been developed. Gas equilibrated buffers are convenient, but even a buffer solution of complex composition is not the same as whole blood. Aqueous control solutions have a lower temperature coefficient than that of whole blood, but this can be minimized if the electrodes are maintained at 37°C, and the tonometry is also carried out at this temperature.

Tonometry, whereby freshly drawn blood is equilibrated with gas mixtures of known P_{O_2} and P_{CO_2} , provides the most rigorous method of quality control blood gas tension measurements. However, this procedure is not easy, and cannot be practically

used to predict the pH values of the blood samples produced. Thus the recent commercial development of a stable liquid containing human red blood cells, prepared in a sterile ampoule, so providing a once only source of calibration for both pH, P_{CO_2} and P_{O_2} electrodes appears very promising. These solutions, which, needless to say, are expensive, can also allow total haemoglobin, oxyhaemoglobin, and carboxyhaemoglobin measurements to be calibrated.

Arterial oxygen saturation can be derived from measurements of P_{O_2} and pH, if the position of the oxygen dissociation curve is either known, or can be assumed. Alternatively, direct measurements of arterial oxygen saturation can be made, by independent instruments which rely upon spectrophotometric analysis of the colour of either reflected or transmitted light of the blood sample. Similar readings at different wavelengths can be used to measure oxyhaemoglobin and methaemoglobin (as in the IL co-oximeter). However, one of the most important advances in this field has been the development of an accurate, stable, non-invasive measurement of arterial oxygen saturation, by ear oximetry.

Although this principle has been known for many years, most previous instruments were relatively difficult to calibrate and were notoriously unstable in practice. The development of a microprocessor-controlled instrument, using a fibre-optic light source to measure the transmittance of the ear at eight different wavelengths, so allowing direct computation of the arterial oxygen saturation with a digital readout, has been a significant advance in this field. This instrument, the Hewlett-Packard 47021A ear oximeter, provides a reliable measurement within $\pm 2\%$ of the measured arterial oxygen saturation down to a level of 60%, but thereafter reads too low, although calibration graphs have been published (Figure 3, Douglas, Brash, Wraith, Calverley, Leggett, McElderry & Flenley, 1979) which allow this error to be corrected.

End-tidal P_{O_2} and P_{CO_2} measurements can be used to provide approximate estimates of arterial P_{O_2} and P_{CO_2} levels, without resort to invasive needling to measure arterial blood gas tensions directly. The principle underlying this use of these measurements is that the terminal portion of a normal tidal breath contains gases which have come from deep within the alveoli, and are thus in close approximation to the P_{O_2} and P_{CO_2} of the blood leaving these alveoli, with which they have been equilibrated. To make these measurements it is desirable to have a rapidly responding gas analyser, sensitive to both P_{O_2} and P_{CO_2} , and this is usually provided by a mass spectrometer. Modern respiratory mass spectro-

Table 1 Manufacturers' specifications of commercially available equipment for automated blood gas analysis (1978)

Manufacturer Measures	IL 613 Instrumentation Laboratory	ABL 2 Radiometer, Copenhagen	Corning Medical Corning 175	AVL 938 AVL AG Biomedical Instrument
Calculates	pH, P_{CO_2} , P_{O_2} HCO_3^- , TCO_2 , B.E. Std. B.E. Std. HCO_3^-	pH, P_{CO_2} , P_{O_2} , Hb barometric pressure HCO_3^- , TCO_2 , B.E. Std. B.E. %HbO ₂ , Std. HCO_3^-	pH, P_{CO_2} , P_{O_2} barometric pressure HCO_3^- , B.E. O_2 content %HbO ₂	P_{O_2} , P_{CO_2} , pH HCO_3^- , B.E. Buffer base, TCO_2 , %HbO ₂
Corrections	Can dial in Hb and patient temperature	Can dial in patient temperature	Can dial in patient Hb and temperature	Can dial in Hb
Heating Sample	Water bath 200 μ l or 125 μ l by suction	Circulating warm air 200 μ l injected	Solid state 500 μ l or 125 μ l by injection	Water bath 25 μ l or 40 μ l by capillary action
Calibration	Uses humidified gases and buffers	Uses equilibrated buffers only. Cannot measure gaseous samples	Uses humidified gases and buffers	Uses humidified gases
Frequency of automatic calibration	Every 20 min carries out a 1-point calibration	Every 2 h carries out a 2-point calibration	Calibrates every 0.5 h—alternates a 1-point and 2-point calibration	Not given
Frequency of flush	Only after sample	Every 7 min and after samples	After sample and if no sample for 5 min, solution is pumped into electrode chamber to condition membrane	Cleaning and drying of measuring capillary is under operator control
Precision	pH ± 0.0022 $P_{CO_2} \pm 0.51$ mmHg (± 0.067 kPa) at $P_{CO_2} = 36$ mmHg $P_{O_2} \pm 1.20$ mmHg (± 0.16 kPa) at $P_{O_2} = 87$ mmHg n = 20	pH ± 0.003 $P_{CO_2} \pm 1.8\%$ $P_{O_2} \pm 0.5$ mmHg (0.066 kPa) at 80 mmHg ± 3.0 mmHg (0.4 kPa) at 400 mmHg	pH ± 0.003 $P_{CO_2} \pm 0.5$ mmHg (0.066 kPa) at 35 mmHg ± 0.8 mmHg (0.107 kPa) at 71 mmHg $P_{O_2} \pm 0.8$ mmHg (0.107 kPa) at 86 mmHg ± 3.8 mmHg (0.506 kPa) at 250 mmHg	pH ± 0.002 $P_{CO_2} \pm 0.1\%$ $P_{O_2} \pm 0.1\%$

Figure 3 Relationship between recorded ear oximeter value and arterial oxygen saturation as directly measured, in 465 simultaneously taken samples. The line is that of identity (from Douglas *et al.*, 1979).

meters are now reliable and sensitive instruments with an adequate time response, although undoubtedly they are expensive. A very small continuous sample of gas is drawn at the patient's lips, and this registers continuously the inspired and expired CO_2 concentrations, or tensions. The usual trace shows a level indicating the inspired tension, rapidly changing to the so-called alveolar plateau, which is usually

parallel to the base-line for the CO_2 trace, but often slopes downwards in the case of the oxygen trace (Figure 4). It is essential that this plateau form should appear before the highest (in the case of P_{CO_2}) or lowest (in the case of P_{O_2}) readings are taken as the end-tidal tensions, for if the patient has taken a breath of insufficient depth to wash out this dead space the plateau level is never achieved, and it is then impossible to interpret the end-tidal tensions as approximating to the arterial blood tensions. Furthermore, end-tidal sampling is only of value as an indication of the arterial gas tensions in a subject with *normal* lungs, for regional and stratified homogeneity in gas distribution, present to some degree even in normal lungs, and thus accounting for the sloping plateau of the oxygen trace, can be very much exaggerated in lungs which are the seat of disease, thus invalidating end-tidal tensions as indicators of arterial tensions in such patients. This stricture applies particularly in patients with chronic bronchitis and emphysema, or in an attack of asthma or pulmonary oedema, etc.

The end-tidal to arterial P_{CO_2} gradient is usually regarded as zero, although various estimates of between + and -2 mmHg (0.3 kPa) have been recorded, but such values probably lie within the accuracy of the recording instruments. However, in the case of oxygen, the small fraction of blood which is shunted from the right side of the heart to the left side without passing through ventilated alveoli, even in normal lungs, means that the end-tidal oxygen tension is always higher than the arterial oxygen tension. This alveolar to arterial oxygen tension

Figure 4 Continuous records of P_{O_2} and P_{CO_2} at the lips, as measured by mass spectrometer, in a healthy subject (male, 27 years) during treadmill exercise when breathing 18% oxygen. IN, inspiration; EX, expiration.

gradient ($A - a P_{O_2}$) is usually around 10 mmHg (1.3 kPa) and is always less than 20 mmHg (3.0 kPa) in health. Nonetheless the uncertainty as to the ($A - a$) P_{O_2} does diminish the accuracy of end-tidal tensions as to measurements of arterial oxygen tensions in practice, and it must again be stressed that these measurements are only of value in patients with normal lungs. As the ($A - a$) P_{O_2} varies with the inspired oxygen tension, this further renders measurements of the end-tidal oxygen tension a relatively uncertain guide to the absolute level of arterial P_{O_2} , even in normal subjects who are not breathing air.

Measurement of the end-tidal CO_2 tension alone usually requires less complicated apparatus than a mass spectrometer. A rapidly responding respiratory infra-red analyser (e.g. Beckman L-B1 infra-red analyser or the Hartman and Braun URAS Capnograph) is widely used to measure the arterial P_{CO_2} by the non-invasive measurement of the end-tidal P_{CO_2} . Again, the same strictures about the presence of the plateau on the resulting trace of the instantaneous expired tensions at the lips apply. It is thus usually desirable to see the actual form of the recording to ensure this to rely only on the 'end tidal' value indicated by the sophisticated electronic circuitry, which usually accompanies modern instruments.

Transcutaneous P_{O_2} measurements are now available, with several commercial electrodes which essentially consist of heated polarographic electrodes which are firmly applied to the skin. These provide a continuous read-out of P_{O_2} , which is usually related fairly constantly to the arterial P_{O_2} in an individual patient, and can be used to give an indication of

transient changes in arterial P_{O_2} . These instruments have mainly been developed for use in neonates, where the thin neonatal skin imposes less barrier to diffusion of oxygen from the underlying arterialized capillaries to the electrode. In the adult the use of such electrodes is still experimental, as is the use of a recently introduced ear P_{CO_2} electrode which depends upon measurement of the CO_2 diffusing through skin from the arterial blood. No doubt further developments in these non-invasive techniques will improve their accuracy and reliability.

Although direct arterial puncture remains the most certain way of obtaining arterial blood and thus arterial blood gas tension measurements, this procedure is invasive, and by its nature can only provide intermittent measurements. Nonetheless, the modern automated blood gas electrodes, which are stable, and require little training in use to obtain accurate results, have an important place in the correct management of clinical problems of respiratory failure and acid base disturbance. However, it seems that the major advance in this area will be further use of the non-invasive methods which give continuous measurements, and this has already, for example, yielded important information on transient hypoxaemia during sleep, particularly in adult patients, as well as important information on the occurrence of hypoxaemia in infants. There is so far no indication that the problems of providing non-invasive measurements of arterial pH have been solved.

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