Review Article

Measurement of Blood Oxygen Tension in Anesthesia

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Adequacy of pulmonary ventilation, whether in awake or anesthetized individuals, receives objective assessment only by measurement of oxygen and carbon dioxide concentrations in arterial blood. Conclusions based on gas concentrations obtained from the airway cannot be transposed into blood concentrations unless thorough knowledge of the ventilation-perfusion relations is at hand.

Uneven distribution of gas and blood to the gas exchanging surface appears to be the rule during anesthesia 15, 16, 27, 47, 68, 120, 122, 123, 151, 162 and is likely to be present in patients requiring mechanical assistance secondary to acute respiratory insufficiency. These factors make the determination of arterial blood gases mandatory.

Oxygen, the primary metabolic fuel, must be supplied to the tissues at an adequate rate in terms of number of molecules (gas content) and driving force (gas partial pressure) to allow for appropriate diffusion.35, 83 The process is facilitated by hemoglobin which insures uptake and transport of considerably greater amounts of oxygen than would be allowed by simple solution.

Included in this review are the physical principles underlying use of the oxygen electrode,* the degree of accuracy to be expected in its clinical performance and its limitations due to unresolved biological problems. A brief survey of its history will place major emphasis on the developments of the past decade. Far more important, it will consider accumulated evidence suggesting that knowledge of the arterial oxygen tension provides a sensitive indicator of ventilatory changes not readily recognized by other routine clinical procedures such as the chest roentgenogram, percentage hemoglobin saturation, tidal volume or arterial carbon dioxide concentrations. Considerable personal experience with the oxygen electrode in clinical and research problems has resulted in several modifications of technique. They are presented in the hope that further use of the oxygen electrode in the study of respiratory problems in anesthesia will be thereby facilitated.

A full discussion of oxygen exchange and alveolar-arterial oxygen gradients during nonsurgical conditions is not possible within the limits of a brief review. We hope that the need for further studies of oxygenation during anesthesia and surgery, defining the extent to which procedures we carry out may be detrimental to the patient in the postoperative period, will be readily apparent. Recent findings on the state of oxygenation during anesthesia will be considered with a brief analysis of causative factors. The source of apparent discrepancies suggested by several authors will be attributed to the multifaceted appearance of hypoxemia in clinical practice.

Basic Principles of O₂ Tension Measurements

The principle relating the partial pressure of a gas to the amount going into solution was formulated by Henry in 1803.76 Most gases when dissolving in water or dilute electrolyte solutions obey Henry’s law, and exhibit a linear relationship between gas tension and the number of molecules in solution when temperature remains constant. Sendroy, Dillon and Van Slyke 147 have shown that solution of oxygen in plasma and whole blood exhibits similar properties. The specific value relating

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tension of a gas to the number of its molecules in a particular solution is known as the Bunten solubility coefficient ($\alpha$), defined as the milliliters of gas going into solution per ml. of fluid, at a specific temperature and a partial pressure of the gas above the fluid of 760 mm. of mercury, the gas volume being corrected to $0^\circ$ C. and standard pressure (i.e., 760 mm. of mercury). The significance of the solubility coefficient will be discussed in relation to calibration of the oxygen electrode and the problems of temperature correction.

The oxygen detecting device consists of a platinum surface (e.g., cross-section of fine platinum wire) to which an appropriate negative voltage is applied via a battery (between 0.5 and 0.8 volts), a silver wire acting as the positive terminal, or anode. Electrical contact is made by immersing both terminals in an electrolyte solution (e.g., potassium chloride, sodium chloride, etc.). When oxygen molecules, present in the electrolyte solution, diffuse to the polarized platinum surface, electrolysis (i.e., decomposition into separate ions by electrical current) of the oxygen occurs, probably by the following reactions:

$$O_2 + 2H_2O + 2e^- \rightarrow H_2O_2 + 2OH^- \quad (1)$$
$$H_2O_2 + 2e^- \rightarrow 2OH^- + 2H^+ \rightarrow 2H_2O \quad (2)$$

These reactions are thought to be irreversible and unless oxygen is continuously supplied to the electrode all oxygen will be ultimately consumed, the rate being dependent, among other things, on the area of the platinum surface. The breakdown of oxygen alters the conductivity of the electrolyte solution and the resulting current can be recorded on an appropriate measuring device.

Immersion of bare platinum wires into blood is followed by the deposition of protein on the platinum surface, which interferes with the steady diffusion of oxygen to the electrode. Until recently, this problem prevented the adequate measurement of oxygen tensions in biological media. The solution was provided in 1953 when Clark et al. demonstrated that isolation of the electrode and electrolyte system from the blood by means of thin, gas permeable plastic membranes permitted repeated determination of the oxygen tension without the attendant difficulties otherwise imposed by the blood proteins. Figure 1 indicates the basic principles operating with the membrane covered electrode.

Since Henry's law establishes a linear relationship between partial pressure and molecules of gas in solution, changes in partial pressure will also exhibit linearity when related to current output, assuming of course that temperature remains constant. With this in mind we can recognize the following factors as determinant of the current magnitude (i.e., the slope of the line relating current and
Fig. 2. Effect of temperature on sensitivity (ampere/millim. of mercury $P_{O_2}$) demonstrated with water equilibrated with three concentrations of $O_2$ (8.5, 16.4 and 20.9 per cent). Equilibration and measurement were carried out at 4 different temperatures using two 0.001 inch platinum electrodes (A and B). By definition, an electrode exhibiting linearity must demonstrate identical sensitivities at all oxygen tensions. This is seen at 25° C., 30° C. and 35° C. in the lower left hand graph. At 40° C. sensitivity falls as the $P_{O_2}$ rises and this is characteristic of an electrode that is not linear. Note: (1) that the relation between temperature and log sensitivity is linear; this permits temperature compensation for an in-circ electrode once its characteristics have been defined; (2) that linearity is not an attribute of all electrodes. In A deviation from linearity increases with rising temperature (bottom) but is not immediately apparent when using a gross plot as in the top portion of the graph; (3) that, if the zero point is not taken into account (top right), apparent linearity can be obtained. Slope of the log sensitivity versus temperature line (also known as the activation energy of the membrane) is determined by the diffusion characteristics of the membrane. Linearity (i.e., sensitivity in amperes/millim. of mercury $P_{O_2}$) over the $P_{O_2}$ range employed (0 - 155 millim. of mercury) is electrode dependent.
concentration of $O_2$: 1) surface area of the platinum cathode, 2) temperature at which the measurement is made (see also fig. 2), and 3) diffusion characteristics of the solution surrounding the electrode and the membrane separating it from the sample.

Increasing of the platinum area results in an increased rate of oxygen decomposition and greater electrode sensitivity (i.e., current developed per mm. of mercury $P_{O_2}$ will be high). High sensitivity despite its apparent advantages, poses definite limitations for an in-vitro system where the total number of $O_2$ molecules is limited, because diffusion to the electrode surface may not keep up with the breakdown rate. The result is absence of a consistent reading, which is required for establishing a good end point for any particular oxygen concentration and calibration line. This difficulty can be overcome if fresh samples of blood, or fluid, are continuously renewed at the electrode surface, either by insuring flow of blood past the electrode, or by stirring of the sample. Simplicity in practice has been achieved by using a low sensitivity electrode in combination with a stationary sample. As we shall see below, such systems have found widespread preference.

With bare platinum electrodes, whether immersed in a solution or implanted in tissues, the problem of calibration is complicated by the relationship between the $O_2$ solubility, $O_2$ content and diffusion characteristics of the media. Reference to figure 3 will clarify the point. Quantitative changes using bare electrodes are difficult if not impossible to evaluate, since correct calibration would require using the same tissue fluid as the one in which the measurements are made. For further analysis of the problem the reader is referred to other recent reviews on the subject.31, 47

Difficulties with the accuracy of in-vitro measurement may be introduced by using very small, or so-called microquantities of sample. This can be characterized as follows:

$$P_{O_2} = \text{partial pressure of } O_2$$
$$a_{O_2} = O_2 \text{ solubility coefficient (Bunsen) of a particular fluid}$$
$$V = \text{volume of fluid}$$

$G$, $H_2O$ and $KCl$ = referring, respectively, to gas, water and potassium chloride

$T$ = temperature

The dissolved $O_2$ content of any fluid (i.e., the portion not combined chemically) can be expressed as follows:

$$O_2^T \text{ content} = a_{O_2}^T \cdot V \cdot P_{O_2} \cdot \frac{1}{760} \quad (3)$$

where $P_{O_2}$ is the partial pressure of oxygen of the equilibrating gas. If a sample of water equilibrated with $P_{O_2}$ is placed in a cuvette containing the electrode, electrolyte and separating membrane, and if the contents of this system are free of $O_2$ before the sample is introduced, the following relationship must hold, after introduction of the sample and equilibration in the cuvette:

$$O_2^T \text{ content (H}_2O) = \left[ a_{O_2}^T \cdot V_{H_2O} \cdot P_{O_2}^T \right] \text{ content of sample outside cuvette} + \left[ a_{O_2}^T \cdot P_{O_2}^T \cdot V_{KCl} \right] \text{ content of sample inside cuvette}$$

$$+ \left[ a_{O_2}^T \cdot P_{O_2}^T \cdot V_{KCl} \right] \text{ content of electrolyte} \quad (4)$$

The final oxygen tension in the cuvette ($P_{O_2}^T$) will depend on the number of $O_2$ molecules given up by the sample in order to saturate the electrolyte not in the immediate vicinity of the platinum surface. Obviously this value cannot be considered equal to the $O_2$ tension of the equilibrating gas.

Care must be exercised before accepting the validity of in-vitro measurements using micro-volumes of sample. Referring to equation (4), if the volume of sample equals the volume of electrolyte, oxygen must move out from the sample into the electrolyte; therefore, the error of measurement will depend on how closely the $P_{O_2}$ of the electrolyte approximates that of the sample prior to introduction of the latter into the cuvette. This problem can be resolved by maintaining a very high sample volume to electrolyte volume ratio and pre-equilibrating the electrolyte by washing out with one aliquot of the sample before introducing the amount from which the actual determination will be made.
The additional effects introduced by $O_2$ taken up into the walls of the cuvette, rubber fittings, membrane, etc., will compound the problems illustrated in equation (4).

**Historical Development**

Techniques for measuring the oxygen content of whole blood were evolved a little over a century ago. In 1837 Magnus reported values for oxygen, carbon dioxide and nitrogen after vacuum extraction from whole blood in vitro. Carbon dioxide was determined by the weight change of sodium hydroxide and $O_2$ by the combustion of hydrogen bubbled through blood. In an extensive paper on methods of gas extraction (boiling in vacuum) Lothar Meyer established the applicability of Henry's law to whole blood at several temperatures, and demonstrated the chemical binding of oxygen to hemoglobin. Direct estimation of the partial pressures of gases in whole blood was first made possible by Pflüger. Blood was introduced into a tonometer containing gases of known concentrations and analysis of the gas phase was made after equilibration between blood and gas had taken place. Many variations of this technique were subsequently introduced depending on the needs of the particular investigator. Thus, in 1879, Herter using Pflüger's method reported a mean arterial oxygen tension of 78.7 mm. of mercury in dogs, while Fredericq found this value to vary between 12 and 14 per cent of an atmosphere.

In 1898 Haldane first noted the ability of ferricyanide salts to displace the oxygen from its chemical combination with hemoglobin. This led to rapid improvement of the vacuum extraction methods and culminated in the manometric technique of Van Slyke and Neill which has dominated the laboratory measurement of blood oxygen contents for almost half a century. However, for $O_2$ tensions above ambient the technique requires separation of plasma from cells and assumption of an $O_2$ solubility coefficient which may vary considerably between samples.

A brief consideration of the difficulties involved will clarify the problem. The major portion of the $O_2$ content measured by this technique consists of oxygen chemically bound to hemoglobin. At partial pressures above full saturation of hemoglobin the changes between $O_2$ content and tension are related by the solubility coefficient ($a$) of oxygen for whole blood. Thus, if we are to utilize a change in $O_2$ content as an indicator of partial pressures of oxygen at the high values we must, by necessity, rely on a small difference between two large numbers, thereby severely limiting its accuracy. Above full saturation of hemoglobin plasma and red cell $P_{O_2}$ are presumably in equilibrium. Therefore, the oxygen content of anaerobically separated plasma must equal the product of $O_2$ tension and the solubility coefficient ($a$) of plasma.

Danneel, the first to use the platinum cathode for oxygen tension measurements, demonstrated a linear relation between $O_2$ pressure (152 to 769 mm. of mercury) and the recorded current. Subsequent work with this device was limited primarily to clarification of the chemical reactions occurring at the platinum surface. Objection to its use in the
clinical laboratory rested on the rapidity with which function was lost when immersed in biological media, due to deposition of protein films on the platinum surface.

Interim studies of oxygenation were carried out with the dropping mercury cathode. This requires measurement of current output changes produced in the test solution while potential (voltage) variations are applied via small drops of mercury (cathode). The latter are allowed to fall through the solution toward another layer of mercury (anode). Electrolytic decomposition of the test substance (e.g., oxygen) occurs only at the mercury drop-solution interface and a voltage characterized by a plateau (increasing voltage, no change in current), on the voltage-current curve. Simultaneous automatic recording of both parameters is possible with a device named a polarograph by Heyrovski in 1925. Excepting the plateau, current changes in proportion to the voltage both below and above this region.

Berggren, Wiesinger, Baumberger, and Beecher, Follansbee, Murphy and Craig used the dropping mercury electrode to measure the oxygen tension in blood and other body fluids. The technique is difficult to master and must be carried out on an anaerobically separated plasma, not whole blood. Bartels varied the applied voltage in order to maintain a constant current at all P O2 values (potentiometric technique) which made possible the direct analysis of oxygen tensions in whole blood. It, too, failed to answer the need since the variable effect produced by the presence of red cells required calibration with aliquots of the sample to be measured.

Use of stationary bare platinum electrodes in flowing liquids and biological media have been described in detail by several authors. Morgan and Nahas applied a fine film of silicone to the platinum surface of a rapidly rotating electrode (described earlier by Kolthoff and Laitinen) in the hope of preventing deposition of the protein. Readings were reported to be related linearly to whole blood P O2 in a range from 50 to 250 mm. of mercury but interference by changes in P CO2 could not be eliminated. Dreneck-hahn reported on the use of a colloison covered platinum wire (diam. 0.15 mm.) for measuring P O2 in defibrinated whole blood. A satisfactory linear relationship was obtained over a P O2 range from 0 to 700 mm. of mercury that did not appear to be influenced by varying carbon dioxide tensions. The standard error about the mean calibration curve was reported to be 2 to 4 mm., an accuracy as yet unsurpassed at high tensions. Efforts to provide reliable continuous measurement of oxygen tension in vivo were recorded by Williams using a vibrating mercury electrode in a flow-through cuvette and an otherwise conventional polarograph, a system previously described by Clements and Moore. Like most systems available at the time (and many available today) calibration in vivo was difficult and required correction factors for both high and low oxygen tensions.

A major advance in whole blood oxygen tension measurements was achieved by Riley, Proemmel and Franke in 1945, with the bubble-equilibration technique. A small amount of blood, its volume accurately measured with a Roughton-Scholander syringe, was equilibrated with a tiny bubble of known volume and gas composition. After equilibration between blood and gas phases had taken place, CO2 and O2 were absorbed from the gas phase with the addition of appropriate reagents, the volume of the bubble being recorded each time. With practice, the method proved to be highly accurate for oxygen tensions up to those in room air. Higher P O2 levels could not be determined.

In 1953, Clark, Wolf, Granger and Taylor reported the first successful application of the membrane covered platinum electrode to the in-vitro and in-vivo measurement of oxygen tensions in whole blood. By separating the electrode and electrolyte from the blood in a manner that allowed only access of oxygen, the problem of instability due to the protein reaction appeared to be solved. The platinum electrode was large (no. 20 B & S gauge—approx. 0.07 cm. in diameter) and required active motion of the blood sample in order to insure a continuous and adequate supply of oxygen to the electrode surface. The first commercial electrode was in fact based on the subsequent work of Clark.

Severinghaus and Bradley defined the
factors affecting performance in vitro of a Clark electrode which required stirring with a small nylon paddle to insure steady diffusion of oxygen to the highly sensitive electrode (i.e., large platinum surface area). Variations on the stirring theme have been published by Bishop,20 (glass coated soft iron slug) Nousi, Sjöstedt and Caligara 21 (stainless steel blade) and Gleichmann and Lübbers 22 (glass coated iron rod). High speed rotation of the entire electrode was utilized by Kreuzer, Watson and Ball 23 to achieve turbulence for optimal gas transfer from sample to the electrode surface.

Elimination of stirring or motion of the electrode appeared as desirable changes in order to simplify the aforementioned mechanical complexities. Of the possible compromises, reduction of the platinum size and increased membrane thickness, have been tried and found successful. Polgar and Forster 24 chose to retain the large platinum electrode but used a membrane relatively impermeable to gas (0.0064 inch thick Mylar polyester). The output of the electrode was reduced to 1/20 of the value obtained when using a polyethylene film. Output differences were still recorded between stagnant and flowing samples (they probably always will be with presently available systems), a plateau being reached at a flow rate of 2.5 ml./minute. The coefficient of variation for $P_{O_2}$ was reported to be approximately 2 per cent (i.e., 14 mm. of mercury at 712 mm. of mercury).

A similar principle was incorporated in the electrode of Bartels and Reinhardt,12 i.e., a relatively large platinum surface (0.1–1.0 mm.) and a poorly permeable membrane (polystyrene applied to the electrode surface as a 1 to 10 per cent solution in carbon tetrachloride). Standard error about the mean in the $P_{O_2}$ range of 4 to 100 mm. of mercury was claimed to be less than 1 mm. of mercury. Application of the membrane was cumbersome (polystyrene drying from solution) and the resulting variations in thickness did influence linearity of the electrode up to $P_{O_2}$ values of 100 mm. of mercury (see figure 5 in the paper by these authors).

Daly, White and Bamforth 13 reported their experience with an arrangement similar to that described by Bartels and Reinhardt,12

![Fig. 4](image)

**Fig. 4.** A: Exploded view of electrode and flow-through cuvette. After dipping the electrode in 3 per cent KCl, the membrane (0.0006 inch polypropylene) is stretched over the electrode and held in place when the tapered washer (W) slides into position, as in B. Cuvette was made from a $\frac{1}{4}$ inch T-tube brass fitting (Swagelok). B: Electrode mounted in cuvette; arrows indicate direction of blood flow. C: Magnified view of electrode surface.

The standard deviation over a $P_{O_2}$ range of 0–700 mm. of mercury was stated to be 7.4 mm. of mercury. In spite of this unusually great accuracy, it is unlikely that electrodes of this type will find great favor due to the great variability involved in application of the membrane. Charette 25 designed a platinum microelectrode (surface area 0.075 mm.²) with a covering membrane formed from dissolved polyethylene. He recognized that the thickness of the membrane affected both the performance of the electrode and the interpretation of results. It is difficult, however, to understand why he concludes that an electrode
with a thick membrane will give a reading which “represents O₂ tension far more accurately than O₂ concentration.” O₂ tension and content will be related according to the O₂ solubility coefficient, while the membrane will affect primarily the O₂ diffusion, and therefore sensitivity characteristics of the system.

Staub 159 described an electrode using 0.002 in. diameter platinum wire and a Teflon membrane 0.00025 in. thick. This represents a compromise between low O₂ consumption rate (small diameter platinum) and high O₂ diffusion coefficient (thin Teflon membrane) in order to obtain a rapid response (90 per cent response in 1 second) and adequate stability. As expected, with a thin and highly permeable membrane, pressure and flow sensitivity were conspicuous. Further reduction in the pressure and flow artifacts has been achieved by Fitt 154 with the smallest platinum wire electrode (0.00004 inch, diameter) reported to date.

Thews 163 proposed a microtechnique for O₂ tension measurements using ear lobe blood collected in small, heparinized glass tubing (volume: 0.06 ml.). The standard deviation of duplicate samples was reported to be ± 1 to 2 mm. of mercury and agreed within 2 mm. of mercury when compared to O₂ tensions of simultaneously drawn arterial samples. The author emphasized the need for doing the determination immediately following sampling, which certainly limits its clinical value, transport between bedside and laboratory being notoriously unreliable. Similarly, Laughlin, McDonald and Bedell 92 have developed a microtechnique for P₁₂ in “arterialized ear lobe blood” by allowing the blood sample to drop onto the surface of the membrane covered electrode (10 μl. sample dropped from a 1 mm. (outside diameter) coagulation tube into an upright Beckman macroelectrode). Although there appeared to be good agreement between the P₁₂ of arterial blood and that obtained from the warmed ear lobe (standard error of the estimate: ± 4.7 mm. of mercury) poor correlation was found when the patient was in circulatory collapse, when the cardiac output was low or when inadequate warming of the ear lobe had preceded sampling. No data for P₁₂ values above 150 mm. of mercury were presented.

Systems permitting continuous measurement of O₂ tensions within a blood vessel or in a pump oxygenator have also been developed. Krog and Johansson 84 mounted the platinum and silver elements at the tip of a cardiac catheter and used an appropriate polyethylen ring to secure the Teflon membrane in place.
Kreuzer, Harris and Nessler reported on the use of catheter-type electrodes in dogs. There appeared to be no relationship between the deflection of the electrode reading and the absolute pulsatile pressure. However, rapid blood pressure changes caused appreciable variations in the P\textsubscript{O\textsubscript{2}} readings. Montgomery, Paton, Lucero and Swan described an electrode system to be used as a monitoring device in a pump oxygenator. Appropriate construction material and use of Teflon membranes made autoclaving possible, an advantage when sepsis is necessary. These authors stated that under experimental and clinical conditions, the electrodes are “not affected by changes in temperature or pressure in the blood.” Lack of accompanying data does not permit assessment of this impression. By including a thermistor in the O\textsubscript{2} electrode flow-through cuvette Meredith, Artesani and Mamlin constructed a temperature compensated oxygen monitoring device. Again, no data was included to indicate the limitations of the system in terms of accuracy with temperature changes. Considerations of this type are limited by the lack of acceptable temperature corrections for blood oxygen tensions performed in vivo (see below). We have utilized a solid electrode, patterned after the type designed by Glover, and mounted in a flow-through cuvette that allowed continuous monitoring of arterial P\textsubscript{O\textsubscript{2}} in experimental animals (fig. 4). The disadvantages of the system include the need for heparinization of the animal and permanent ligation of the cannulated artery. A more recent model, uses a Teflon membrane (0.00075 or 0.001 inch thick), can be autoclaved and has found limited clinical use in a pump oxygenator (fig. 5). Its temperature sensitivity (i.e., current output in amperes per mm. of mercury P\textsubscript{O\textsubscript{2}} for a particular oxygen tension at various temperatures) can be defined when one is dealing with P\textsubscript{O\textsubscript{2}} values well above the full saturation of hemoglobin, i.e., probably above P\textsubscript{O\textsubscript{2}} of 200 mm. of mercury at 38°C (see also fig. 2). When saturation is incomplete, readings obtained in vivo during changes in temperature appear to lose their meaning and we have been consistently disappointed when comparing values in vivo with simultaneous samples measured in vitro and corrected from 38°C.

In our experience, commercially available electrodes for in-vitro work are not consistently linear, evidence for this problem being presented in figures 2A and B. A straight calibration line between partial pressure of O\textsubscript{2} and current output, temperature being constant, implies that the sensitivity of the electrode (i.e., amperes/mm. of mercury P\textsubscript{O\textsubscript{2}}) must remain constant over the full range of oxygen concentrations. Actual measurements of sensitivity between zero and 20.03 per cent O\textsubscript{2} at different temperatures suggests that such linearity may be more apparent than real, particularly if only a few points are determined on a concentration versus current plot. Validation of any instrument must, therefore, include an assessment of this relationship. The slope of the line relating current sensitivity to temperature at a constant tension of O\textsubscript{2} is dependent on the so-called activation energy, or diffusion characteristics of the plastic membrane. However, once this relationship has been established it should be possible to correct for temperature variations in vivo by the inclusion of compensating thermistors and electronic circuits for adjustment of the current readings.

Granting that this physical problem can be overcome, we are still left with the greater problem of knowing how to adjust for the temperature effect on the oxyhemoglobin dissociation curve. This problem requires further study and the reader is cautioned to exercise skepticism before accepting data obtained with an in-vitro electrode calibrated in vitro.

Reports with intravascular electrodes in man have been published by Said, David and Crosier using a Beckman needle electrode (microelectrode); Koeff, Tsao, Vadnay, Wilson and Wilson using an electrode designed by Tsao and Vadnay; Charlton, Read and Read using a needle electrode from the model originally designed by Charlton; and Cosby et al. using a Beckman microelectrode. Finley has described an extra-vascular flow-through cuvette for measuring arterial P\textsubscript{O\textsubscript{2}} in man. Variations on these devices have been published by others. All suffer from the shortcoming that calibration in vivo with flowing samples of water or saline need not correspond to the response in vivo. Said, Davis and Crosier compared the accuracy of an in situ arterial Beckman microelectrode...
with in vitro measurements performed with the Riley bubble technique. For $P_{O_2}$ values below 100 mm. of mercury the standard deviation of the difference between the two techniques was 2.5 mm. of mercury. Our own in vitro studies have indicated good agreement above $P_{O_2}$ levels of 150 mm. of mercury.\textsuperscript{23}

A recent review of oxygen electrodes not requiring polarization, (so-called galvanic cells) has been presented by Hobbs.\textsuperscript{20} The reader interested in continuous measurement of airway $O_2$ concentrations will find that appropriate instruments have already been designed for this purpose.\textsuperscript{22}

In summary, the state of the art has evolved sufficiently to permit accurate in-vitro measurements of arterial oxygen tension. Various devices have been tried by different workers with equal success. Standardization is badly needed, and once achieved will probably serve to increase the popularity of the technique at the clinical level. Ultimately, we must find a way to combine the known behavior of oxymoglobin dissociation and electrode performance as influenced by temperature into a system which will allow the continuous monitoring of arterial oxygen levels. Reason for this need will be established in the sections to follow. However, it should come as no surprise, considering the fundamental importance of oxygen in bodily functions.

Practical Considerations

Sampling of Blood. Generally we prefer to tap the femoral artery for single samples, except when a clear-cut history of symptoms related to obstructive peripheral vascular disease can be elicited. Percutaneous radial or ulnar artery punctures are performed whenever continuous sampling is required. Needles consisting of an outer plastic (e.g., Teflon) coating and a metal stylet are well suited for this purpose. We have set an arbitrary limit of 48 hours for the time these catheters are allowed to remain in situ. The one major drawback is the discomfort presented by repeated arterial puncture. The difficulty appears to lie more with the residual soreness than the pain of the puncture since the latter can be overcome with local anesthesia.

Individual samples are readily obtained from the artery via a number 20 standard wire guage hypodermic needle into a 5- or 10-ml syringe, presurized with liquid heparin, the dead space being filled with anticoagulant. Oil or mercury are not used since they may alter membrane characteristics. Suitable syringe caps are made by using the hubs of hypodermic needles and adding a drop of solder into the remaining orifice when the needle has been cut away. Disposable plastic syringes (5-ml size) have been found to maintain a high $P_{O_2}$ as well as glass syringes for periods of up to 2 hours. However, if any delay in analysis is foreseen it is best to utilize glass syringes, placed in ice until the measurement can be carried out. One must not forget to note both the patient’s temperature and inspired $O_2$ concentration at the time that the arterial samples are taken. Determinations while a subject is breathing 100 per cent $O_2$ must be made only when the gas is administered with a tight anesthesia face mask, auffed endotracheal, or tracheostomy tube, preferably using a nonbreathing system. Ten to twenty minutes usually suffice to reduce the nitrogen concentration in expired air to 1 per cent or less of the total inert gas.

With high arterial oxygen tensions it is important to perform the determinations as soon as possible after the sample is drawn. At 38° C. the rate of $P_{O_2}$ drop in whole blood following sampling is determined by (a) leakage from the syringe and (b) the $O_2$ consumption rate by the cells. Figure 6 illustrates the problem when fresh heparinized blood is tonometered with 70 per cent oxygen and then maintained in a water bath at 38° C. for a period of 1 hour. The difference between the $P_{O_2}$ of plasma and the control reading represents leakage from the system while the difference between whole blood and plasma indicates the $O_2$ consumption rate of the cells (rate of $P_{O_2}$ loss in whole blood: 2–3 mm. of mercury per minute). This is in agreement with figures quoted by others.\textsuperscript{5} 110, 119

It is not unusual to find postsurgical patients with acute respiratory insufficiency, ventilated mechanically with 100 per cent $O_2$, whose arterial $P_{O_2}$ may be well below 100 mm. of mercury. If the inspired $O_2$ concentration is not recorded at the time of sampling review of the laboratory data at a later date may lead to erroneous interpretation of underlying changes.
The precise temperature at which in vitro blood oxygen tensions are to be measured has not received adequate definition. Standardization is urgently required in order to permit a meaningful comparison of data obtained by various investigators. The alveolar capillary temperature (where equilibration between gas and blood takes place) has recently been evaluated by Edwards, Velasquez and Farhi \(^{23}\) using a highly ingenious technique. Normal subjects were allowed to breathe a known mixture of two inert gases (helium and argon) and the respective contents subsequently measured in arterial blood. Since these gases go into solution, the amounts dissolved in blood will be related as the ratio of the solubility coefficients at the temperature of exposure in the pulmonary capillaries. Consequently, any subsequent changes in temperature, while blood circulated from the lung to the sampling site, could not have altered the ratio of blood gas contents. Pulmonary capillary temperature (\(T_{pc}\)) was found to correlate well with rectal temperature (\(T_r\)) resulting in the following regression equation:

\[
T_{pc} = 37.15 + 2.1(T_r - 37.1)
\]

(5)

According to Afonzo, Rowe, Castillo and Crumpion \(^{1}\) the temperature of pulmonary arterial blood determined in 17 patients by means of an intravascular thermistor varied from 97.78 to 99.35° F. (mean 98.54° F.). Temperatures in the left atrium were found to be a mean of 0.01° F. higher than in the pulmonary artery.

The problem of temperature correction is compounded when analyzing blood sampled during anesthesia, the latter according to Smith,\(^{24}\) being associated with a mean fall of 1.05° C. in esophageal temperature. Greater variations will be encountered during thoracotomy and must be taken into account as affecting the equilibration between gases and blood in the pulmonary capillaries. We do not know whether the relationship established by Edwards, Velasquez and Farhi \(^{23}\) would hold during thoracotomy or general anesthesia.

\(P_{O_2}\) measurements. \(O_2\) tension measurements in our laboratory have been carried out with commercially available electrodes made with platinum wire 0.001 in. or 0.0008 in. in diameter, polypropylene (0.0006 inch) or Teflon FEP (0.0005 inch) membranes and 3 per cent (0.4 N) KCl solution. Addition of phosphate buffer to the electrolyte has been suggested in order to reduce \(pH\) changes arising from the breakdown of oxygen, but in our experience, presence or absence of the buffer has not given rise to recognizable differences in performance. The aforementioned electrodes have a protruding solid glass capillary containing the platinum cathode.\(^{7}\) Instability is most often associated with retained air bubbles or a loosely mounted membrane. Such instability is readily noted as a persistent drift, most conspicuous when using water samples equilibrated with high \(O_2\) tensions (e.g., 70

\(^1\) Beckman macroelectrode manufactured by Beckman Instruments, Inc., Fullerton, California.

\(^2\) Radiometer electrode available through London Co., Cleveland, Ohio.

\[\text{Fig. 6. Freshly drawn heparinized whole blood from normal adult subjects was tonometered at 38° C. with gas containing 70 per cent } O_2 , 5 \text{ per cent } CO_2 \text{ and the balance } N_2 . P_{O_2} \text{ was measured at the end of tonometry and every 10 minutes thereafter, the blood being kept in the interim at 38° C. Plasma, obtained by centrifuging whole blood, was treated in a similar manner. Mean values = S.D. of ten measurements.}\]
per cent \( \text{O}_2 \). In our laboratories, where an average of 30 routine clinical \( P_{\text{O}_2} \) determinations are performed daily, we have found that no commercially available electrode will continue to function after 3 months of daily use. The fault appears to lie in the formation of a short-circuit between platinum cathode and silver anode probably due to infiltration by the strong electrolyte solutions.

Calibration of the electrode is carried out with water equilibrated with 2 concentrations of \( \text{O}_2 \): 20.9 per cent (compressed air) and 70 per cent. A third point of zero \( \text{O}_2 \) is established initially with a sodium sulfite in borax solution (sodium sulfite is a strong reducing substance at an alkaline \( \text{pH} \)), and subsequently with water, equilibrated with nitrogen.† Traces of sodium sulfite are sometimes difficult to wash out of the cuvette and if improperly removed, may lead to changes in \( P_{\text{O}_2} \) of subsequent samples. Consecutive readings at the high end of the curve (above 500 mm. of mercury \( P_{\text{O}_2} \)) should not vary by more than 10 to 15 mm. of mercury (i.e., 2–3 per cent), otherwise improvement in performance must be sought either by changing to a fresh piece of membrane or cleaning the electrode surface with fine powdered pumice. Instability may also result from the presence of small holes in the membrane (particularly with very thin membranes such as 0.00025 inch Teflon) formed during the manufacturing process or while being mounted on the electrode.

McCom and Robinson,104 using a commercial model of the electrode described by Bishop,90 suggested a two-point method of calibration, one being defined as the electrode specific constant (\( K = \text{current obtained from water equilibrated with air divided by the background current at zero \( \text{O}_2 \)) and the second obtained with water equilibrated with air. These authors experienced difficulty with stable readings at high \( \text{O}_2 \) tensions but unfortunately did not comment on the possible sources of the problem. A glance at the upper portion of figure 2B indicates a reason for such difficulties. The electrode used was calibrated with 3 concentrations of oxygen in water and

† Sodium sulfite in borax provides the point of zero oxygen. Commercially available nitrogen is not oxygen free and its true reading may be obtained for subsequent calibrations by reference to the zero point established with the reducing agent.

---

Fig. 7. Method utilized in our laboratory for mounting commercially available electrodes in brass or stainless steel cuvettes for in-vivo oxygen tension measurements. Entire assembly can be immersed in the water bath. Total volume of cuvette between the two female adaptors, with electrode in place: 0.3 ml.

Fig. 8. Water bath containing a cuvette-mounted \( \text{O}_2 \) electrode and the test tubes used for equilibrating water with different \( \text{O}_2 \) concentrations. \( \text{A} = \) oxygen electrode mounted in cuvette. \( \text{B} = \) Seeringhaus \( \text{CO}_2 \) electrode. \( \text{C} = \) test tubes containing water for equilibration with various \( \text{O}_2 \) concentrations. \( \text{S} = \) sample being introduced to \( \text{O}_2 \) cuvette. \( \text{T} = \frac{1}{4} \) inch polyethylene cast tubing delivering \( \text{O}_2 \) gas mixtures.
the point of zero oxygen was set to zero by the addition of sodium sulfite. The three points of 8.5 per cent, 16.4 per cent and 20.9 per cent $O_2$ appear to lie on a reasonably good straight line. However, these lines, regardless of temperature do not pass through the origin, a point which has actually been determined. Furthermore, the point of zero current is affected by temperature, the lines drawn intersecting the abscissa at higher currents with rising temperature. If the calibration had been carried out by using zero and 20.9 per cent $O_2$ the resulting slope of the lines would have been markedly different. This type of response is not readily apparent when using gases for calibration purposes.

The in vitro electrodes are housed in a cuvette which permits insertion of the entire assembly into the constant temperature bath. Standard T-tube plumbing fixtures have been adapted for this purpose. They are inexpensive, easy to clean and sturdy (figs. 7 and 8). Contrary to the experience of others, we have found no differences in performance when using brass or stainless steel cuvettes except for the higher price of the latter. Per-

haps, by immersing the entire unit into the water bath, differences produced by conductivity properties and temperature gradients are eliminated. Electrodes and cuvettes are cleaned between determinations with tap water. No advantage is provided by the use of detergents.

We prefer to calibrate with oxygen equilibrated water in lieu of gas for the following reasons: (1) Trapping of air bubbles in the cuvettes is eliminated. (2) Drying of the membrane does not occur. (Response characteristics of the electrode are more stable when the membrane is hydrated. However, this is preventable by the use of gases fully saturated with water vapor.) (3) Cooling of the electrode surface by flowing gas is prevented (membrane permeability is a temperature dependent phenomenon). (4) Equilibrated water and blood give identical readings in our system; this is not true for gas and blood (fig. 9).

Choice of membranes will be dictated by the particular needs of the investigator. Teflon (0.00025 inch or 0.0005 inch) can

** Commercially available Teflon membranes are made by two different processes. DuPont Teflon FEP (fluoro-ethylenic-propylene) (0.0005
Fig. 10. Accuracy of temperature correction for whole blood assuming that blood has a constant relative solubility over the temperature range indicated (24.5° C to 38° C). (Relative \( O_2 \) solubility = \( O_2 \) solubility in whole blood - \( O_2 \) solubility in water).

Blood was tonometered at one of four temperatures shown and the \( P_{O_2} \) measured both at temperature of tonometry as well as 38° C. Horizontal lines in each panel indicate the \( P_{O_2} \) in the gas phase as determined by the Scholander technique. (By permission from Hedley-Whyte, J. and Laver, M. B.: \( O_2 \) solubility in blood and temperature correction factors for \( P_{O_2} \), J. Appl. Physiol. 19: 501, 1964.)

be autoclaved and provides a rapid response time, but pressure effects are more prominent, probably due to its high elasticity.

Some degree of water permeability is present in all plastic membranes. How this may influence the concentration of electrolyte surrounding the electrode after several hours or days of use remains to be determined. Teflon FEP film has a reported water permeability of 0.4 g/100 square inch (24 hour/mL).

Two milliliters of blood are required for a single determination. One milliliter is injected initially and this serves to saturate the electrolyte membrane, rubber O-ring, etc.: a second milliliter is injected after 30 seconds and the reading taken at two minutes. (Actual cuvette volume + dead space = 0.3 ml.)

Temperature Correction. Until recently the generally accepted temperature corrections for blood oxygen tensions were those published by Bradley, Stupfel and Severinghaus.26, 154 These authors calculated the \( P_{O_2} \) correction factors from data obtained by tonometry of citrated bank blood at different temperatures and various oxygen tensions below full saturation of hemoglobin. The nomogram of Severinghaus utilized higher values for \( P_{O_2} \) (up to 300 mm. of mercury) from data published earlier by Nahas and Wood.117

The effect of temperature on the relative solubility coefficient of oxygen in blood has recently been re-investigated by Hedley-Whyte and Laver.12 Data obtained with two oxygen electrodes maintained at 38° C. and a lower temperature supported Bohr's original hypothesis that the relative solubility of blood for oxygen was constant between 24.5° C. and 38° C. These findings are at variance with the \( O_2 \) solubility versus temperature relation

\[
\text{Relative solubility} = \frac{\text{solubility of } O_2 \text{ in blood at temp. } T}{\text{solubility of } O_2 \text{ in water at temp. } T}
\]
shown in figure 3 of Sendroy, Dillon and Van Slyke and recently reproduced in the "Handbook of Respiration." Furthermore, direct measurement of blood oxygen tensions with the electrode revealed that temperature corrections for \( P_{O_2} \) values read above 200 mm. of mercury at 38° C. could not be achieved with the nomogram of Severinghaus since the error introduced by the assumption that hemoglobin is not fully saturated above this oxygen tension, was found to be large. Temperature correction factors were proposed to replace the available figures at oxygen tensions above full oxyhemoglobin saturation.

The apparent discrepancies reported by Marshall and Gunning with clinical measurements during hypothermia can probably be accounted for by the observations of Hedley-Wythe and Laver (fig. 10).

Available data for \( O_2 \) solubility coefficients (Bunsen) in whole blood are shown in table 1. Since the relative solubility of blood remains constant over the temperature range encountered clinically, corrections may be obtained by multiplying the value of \( P_{O_2} \) read at 38° C. by the ratio of the Bunsen solubility coefficient for \( O_2 \) in water at 38° C. divided by the solubility coefficient for water at temperature (T) of equilibration. The reader is referred to the original paper for details. Below a \( P_{O_2} \) of 200 mm. of mercury, the usual nomogram appears to be valid within certain limitations. Obviously, the effect of various factors on the hemoglobin dissociation curve is in need of further investigation.

**Interpretation of Data Obtained During Anesthesia and Surgery**

Experience with the oxygen electrode before, during and following anesthesia has been

**Table I. Bunsen \( O_2 \) Solubility Coefficients (\( a \)) for Whole Blood (Data from the Literature)**

<table>
<thead>
<tr>
<th>Author</th>
<th>(a)</th>
<th>Temp. of Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer(^{109})</td>
<td>0.018</td>
<td>20.7° C.</td>
</tr>
<tr>
<td>Bohr(^{54})</td>
<td>0.022</td>
<td>38° C.</td>
</tr>
<tr>
<td>Fuscelo &amp; Chiodi(^{37})</td>
<td>0.0261</td>
<td>37° C.</td>
</tr>
<tr>
<td>Sendroy, Dillon &amp; Van Slyke(^{117})</td>
<td>0.023</td>
<td>38° C.</td>
</tr>
<tr>
<td>Hübner(^{41})</td>
<td>0.02486</td>
<td>38° C.</td>
</tr>
</tbody>
</table>

The effect of morphine on tidal ventilation and sighing pattern in a subject with post-operative pain. Tracings obtained with pressure sensitive device placed around the patient's chest. Upstroke = inspiration. The single, large peak to the right in the uppermost channel represents a deep breath and its magnitude is at least 3 times the tidal volume. (By permission from Egbert, L. D., and Bendixen, H. H.: Effect of morphine on the pattern of breathing: a possible factor in the etiology of atelectasis, J.A.M.A. 188: 485, 1964.)

very limited. Hopefully, future studies of oxygenation will correct this state of affairs.

Arterial oxygen tension changes during apnea following ventilation with room air or 100 per cent \( O_2 \) have been followed by Heller and Watson. Although the qualitative occurrence of these changes was recognized prior to the advent of polarography, accurate quantitation of the rate of change was possible only by the measurement of blood oxygen tensions.

**Atelectasis and Intermittent Deep Breaths.** Mead and Collier recognized intermittent deep breathing (sighing) as a part of the normal ventilatory pattern which must be carried out consistently if atelectasis is to be prevented. These authors indicated that dogs ventilated with adequate volumes demonstrated a fall in compliance and functional residual capacity when deep breathing was omitted from the ventilation sequence. Both values returned to normal when a sigh was administered. Spontaneous deep breaths were noted by Bendixen, Smith and Mead to occur with a mean frequency of 8.8 ± 5.5 sighs per hour in awake volunteer male subjects and 10.2 ± 7.1 sighs per hour in females.
Absence of deep breaths is associated with a falling arterial $P_O_2$ in anesthetized subjects breathing spontaneously or ventilated with volumes large enough to maintain normal $P_O_2$.

Alteration of pulmonary geometric integrity causes hypoxemia in patients breathing room air following surgery.42, 122 The fall in compliance, and the rising A-aDO$_2$, when breathing 100 per cent O$_2$ points to progressive, diffuse atelectasis 10, 69, 106 as a cause of the difficulties. Narcotics in the postoperative period appear equally effective in reducing, or eliminating the normal sighing frequency,44 thus perpetuating the low compliance state and the hypoxemia secondary to elevated A-aDO$_2$ gradients (fig. 11).

Atelectasis and Alveolar-Arterial $O_2$ Gradients (A-aDO$_2$). Perfusion of collapsed alveoli can continue for many hours, the magnitude of venous admixture being related to the total cardiac output and the arterio-venous oxygen difference in the so-called shunt equation.51 A graphic representation of this relationship is shown in figure 12. The shunt equation, reproduced at the top of figure 12, and derived in the Appendix, states that when breathing 100 per cent O$_2$ the difference in oxygen content between pulmonary capillary blood exposed to ventilating alveoli and the arterial blood is brought about by admixture of venous blood. Once denitrogenation is complete it may be assumed that the alveolar $P_O_2$ (PAO$_2$) is equal to the barometric pressure minus the water vapor pressure at the patient's temperature, minus the arterial $P_CO_2$. A negligible error is introduced by assuming that arterial and alveolar $P_CO_2$ are equal, even in the presence of a large physiological dead space, due to the comparatively high alveolar $P_O_2$. Figure 12 was drawn on the assumption that the arterial $P_CO_2$ was 40 mm. of mercury and permits a rapid assessment of the effect produced by changes in cardiac output (reflected in the A-aDO$_2$ difference) and the percentage shunt, on the arterial O$_2$ tension.

Normal values for the A-aDO$_2$ during breathing of 100 per cent O$_2$, as collected from the literature are listed in table 2, while the effect of age on arterial oxygen tensions in resting adult subjects breathing room air is shown in table 3.

A small amount of venous admixture occurs normally in man 24, 52, 106 and experimental animals 5, 10 due to (1) anatomical connections between mixed venous and arterial blood which bypass the gas exchange areas, and (2) slight deviations of the ventilation-perfusion ratio from the ideal value. No more than 3 per cent of the cardiac output is shunted through anatomical bypass channels in normal human lungs. Uneven distribution between ventilation and perfusion probably accounts for an equal amount of venous admixture.6, 29 In the presence of lung disease increases in the alveolar-arterial oxygen gradients (A-aDO$_2$) are invariably caused by alterations in the ventilation-perfusion ratio. Such disturbances are prominent in chronic obstructive emphysema 29, 60, 118 and mitral disease.21, 51 A method for determining uneven pulmonary blood flow has recently been de-
scribed by Finley and consists of continuous measurement of the arterial P0₂ from the moment that the subject begins to breathe 100 per cent O₂. The method is based on the principle "that the rate of rise of alveolar O₂ tension during oxygen inhalation depends on the distribution of inspired O₂ to well and poorly ventilated regions of the lung (in relation to their volume), while the rate of simultaneous rise of arterial O₂ tension depends on the distribution of pulmonary blood flow to these regions and the anatomical shunts." This method would provide a rapid assessment of changes in ventilation-perfusion relationships when monitoring patients receiving prolonged respiratory assistance. Its usefulness presupposes an available, sturdy and reliable intravascular electrode. Perhaps such instruments will come into general use in the near future. Björk, Michas and Ugglö have evaluated the arterial O₂ tension at rest and following standardized exercise (bicycle ergometer) as a test of pulmonary adequacy for withstand-sensitive surgery. Exercise had little or no significant influence on arterial P0₂ in patients with low pulmonary reserve, a low P0₂ at rest being associated with a low P0₂ during effort. A positive correlation was found between maximum breathing capacity and resting P0₂ while patients with a high residual volume exhibited P0₂ levels significantly lower than normal.

Measurements of P0₂ in open chest dogs have demonstrated an essentially linear relationship between the A-aDP0₂ and the calculated shunt. Compliance does not appear as good an indicator of lung volume as the oxygen gradient during ventilation with 100 per cent O₂. Farhi and Velasquez produced atelectasis in dogs by means of positive-nega-
tive respiration and noted the absence of a linear relationship between compliance and venous admixture. Using a plethysmographic technique for rapid measurement of the func-

<table>
<thead>
<tr>
<th>Author</th>
<th>A-aDP0₂ (mm. Hg)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berggren</td>
<td>11.3±1.5</td>
<td>Dropping mercury electrode</td>
</tr>
<tr>
<td>Morgan &amp; Nahass</td>
<td>57</td>
<td>Rotating platinum electrode</td>
</tr>
<tr>
<td>Wiesinger</td>
<td>8±1.6</td>
<td>Dropping mercury electrode</td>
</tr>
<tr>
<td>Wilson et al</td>
<td>16±11</td>
<td>Dropping mercury electrode</td>
</tr>
<tr>
<td>Said &amp; Banerjee</td>
<td>26 (7–40)</td>
<td>Membrane covered platinum electrode</td>
</tr>
<tr>
<td>Cole &amp; Bishop</td>
<td>8.0 (20–20 yrs.)</td>
<td>Membrane covered platinum electrode</td>
</tr>
<tr>
<td>Lillehei et al</td>
<td>44.4±19</td>
<td>Dropping mercury electrode</td>
</tr>
<tr>
<td>Polgar &amp; Forster</td>
<td>62.6±15.32</td>
<td>Membrane covered platinum electrode</td>
</tr>
<tr>
<td>Ayres, Criscitelli &amp; Grabovsky</td>
<td>37.1±24.5</td>
<td>Membrane covered platinum electrode</td>
</tr>
<tr>
<td>Fasciolo &amp; Chiodi</td>
<td>35.8±19.6</td>
<td>O₂ content of plasma</td>
</tr>
<tr>
<td>Wood</td>
<td>40±53.2</td>
<td>O₂ content of plasma and blood</td>
</tr>
<tr>
<td>Nunn and Bergman</td>
<td>14.8±55.2</td>
<td>Membrane covered platinum electrode</td>
</tr>
</tbody>
</table>

The table above shows the variations in A-aDP0₂ across different studies.
Once the chest is opened, the inherent tendency of the lungs to collapse is enhanced. In the absence of an imposed resistance to expiration, extensive atelectasis must occur regardless of the tidal volume used. Thus, a waxing and waning of venous admixture appears during the respiratory cycle, its magnitude being dependent on the duration of the expiratory pause. Direct sampling from the pulmonary vein of man has confirmed the persistence of blood flow past freshly collapsed portions of the lung.

The influence of altered end-expiratory resistance or pressure and various airway pressure patterns on the magnitude of the A-a\textsubscript{DO\textsubscript{2}} has been investigated by Frumin, Bergman, Holaday, Rackow and Salanitri\textsuperscript{44} and more recently by Bergman\textsuperscript{19} during short-term studies in man and dogs. Hill, Finley, Takamura, Orallo and Bonica\textsuperscript{29} demonstrated a diversion of blood from a ventilated to an atelectatic portion when the ventilated lung was inflated with pressures exceeding 15 cm. of water in open-chest dogs.

Persistence of blood flow through acutely (as contrasted to chronically) collapsed areas of the lung is not a new concept. In 1869 Powell\textsuperscript{128} reported that in the isolated lung of a dog perfused with "whipped bullock's blood" equal time was required for blood flow through an expanded as through a collapsed portion of the organ, indicating no change in resistance to flow in atelectatic areas. Study of blood flow through collapsed portions of the lung was stimulated, in the earlier part of this century, by the growth of thoracic surgery. The bulk of evidence pointed to persistence of flow in atelectatic areas during the acute stage except when collapse was produced by external pressure on the lung.\textsuperscript{4,21,174} Sackur\textsuperscript{160} was probably the first to make use of the changes in blood oxygen content for determining the quantity of venous admixture and his formula forms the basis for the present-day shunt equation.\textsuperscript{81,121}

The earliest comment found by the authors on the effect of deep breaths on oxygen exchange in the lungs appears in a paper published in 1888 by Geppert and Zuntz.\textsuperscript{25} These authors suggested (p. 231) "that not all portions of the lungs are ventilated evenly; the
well-known crackling breath sounds heard after a deep breath which follows a period of shallow respiration indicates that small segments must have been collapsed during shallow breathing. Blood flowing through such poorly or non-ventilated areas will emerge more venous in character than blood passing through other portions of the lung. One deep breath suffices to produce an equal re-expansion of all alveoli and a consistent improvement in oxygenation of the blood. This is in accord with our repeated observation, made during sampling of arterial blood from resting animals, that one deep breath is followed by a marked change of arterial blood to a brighter color.” (Present authors’ translation.) Magnitude of the anatomical shunt has been assessed in terms of both the classical oxygen tension and content changes as well as with radioactive isotopes.\(^{31, 63, 106, 110}\)

**Atelectasis and Ventilation-Perfusion Abnormalities.** Maldistribution between ventilation \((V_A)\) and perfusion \((Q)\) also contributes to the alveolar-arterial oxygen difference when breathing room air.\(^{6, 52, 96, 93}\) and undoubtedly forms the major portion of the gradient in patients with chronic lung disease.\(^{29, 115}\) It is unlikely that diffusion plays a role in the shunt effect known to occur when a patient is anesthetized unless the inspired oxygen is lowered to hypoxic levels.\(^{141, 153}\) During and following anesthesia and surgery, maldistribution and atelectasis combine to increase the calculated oxygen gradient when patients are breathing less than 100 per cent \(O_2.\) How much atelectasis contributes to the \(A-aD_{O_2}\) can be defined by measuring the arterial oxygen tension when ventilating with 100 per cent \(O_2.\) \(^{11}\) After denitrogenation, alveolar gas will contain only \(O_2, CO_2\) and water vapor; the resulting gradient must therefore be due to venous admixture either via anatomic right-to-left channels or perfusion of collapsed spaces.

Atelectasis \(a\) nonventilated but perfused airspace\(s\) is potentially reversible. Based on all evidence available it is difficult to envisage another mechanism to explain the simultaneous rise in arterial \(P_{O_2}\), functional residual capacity and compliance following a deep breath in a patient ventilated with 100 per cent \(O_2.\) Reversibility of acute ventilation-perfusion abnormalities is a problem that needs further investigation. Both conditions co-exist in anesthetized patients, but from a practical standpoint altered states of pulmonary expansion appear, at least for the moment, more amenable to treatment.

Further understanding of the problem can be obtained by reference to the classical theoretical analyses of Rahn\(^{123}\) and Riley and Courmand.\(^{121, 122}\) Its clinical importance can be illustrated by an inspection of figure 14 which represents a slight variation of figure 12. It is assumed that a safe level of arterial \(P_{O_2}\) in man during anesthesia is given by the value of 100 mm. of mercury. Considering the available data on the percentage shunt likely to occur on the basis of \(A-aD_{O_2}\) gradients,\(^{15, 16, 73}\) we note that in the presence of a normal cardiac output \((A-V_{O_2} \text{ difference } = 5 \text{ to } 8 \text{ volumes per cent})\) a 10 per cent shunt requires an alveolar \(P_{O_2}\) between 250 and 300 mm. of mercury. This suggests that ventilation with any mixture containing less than 50 per cent oxygen narrows the margin of safety, in terms of oxygenation to a point where slight alterations in pulmonary dynamics may easily precipitate hypoxia. Since angina pectoris is known to occur in the absence of cyanosis we cannot rely on indefinite criteria such as skin or blood color for adequacy of oxygenation.

Figure 14 does not take into account the effect of venous admixture produced by disturbances of ventilation-perfusion when breathing less than 100 per cent \(O_2.\) Therefore, the alveolar \(P_{O_2}\) values required to maintain the arterial \(P_{O_2}\) at 100 mm. of mercury are necessarily higher than expected. It is surprising how well this rather simple theoretical approach has been confirmed by recent clinical findings.\(^{42, 120, 122}\)
not defined by the authors) the mean $P_aO_2$ on postoperative days 1 to 5 ranged from 68.5 to 78 mm. of mercury (mean preoperative: 99 mm. of mercury) while in 5 patients with atelectasis the mean $P_aO_2$ on postoperative days 1 to 5 varied between 56.5 and 72.5 mm. of mercury (mean preoperative: 98 mm. of mercury). Although the authors attribute the drop from the preoperative values to atelectasis it is difficult to see how they were able to differentiate arterial oxygen tension changes due to ventilation perfusion abnormalities short of complete alveolar collapse. Taylor, Scott and Donald studied the arterial oxygen tensions of 6 patients undergoing uterine curettage under halothane-oxygen and spontaneous respiration. In the course of anesthesia the $P_aO_2$, varied from 332.8 ± 72.75 to 380.5 ± 107.98 mm. of mercury. This value agrees with the data of Bendixon, Hedley-Whyte and Laver suggesting that atelectasis was present at the time of sampling (breathing a mixture of 95 per cent $O_2$ should result in a $P_aO_2$ of 550 mm. of mercury or higher in patients without lung disease and after adequate nitrogen washout). Since these patients were breathing spontaneously during operation, recovered quickly following cessation of anesthesia, and did not have the type of incisional pain that would interfere with intermittent deep breathing, one cannot be too surprised at the normal postoperative $P_aO_2$ values. In the study of Conway and Payne muscle relaxants were used throughout. This factor plus the extensive surgery are likely to contribute to the postoperative disturbance of ventilation-perfusion ratios and persistence of diffuse atelectasis. The latter authors reported a mean $P_aO_2$ of 83.6 ± 21.6 mm. of mercury, while patients were being ventilated with 6 liters $N_2O$ and 2 liters $O_2$ per minute, a remarkably low figure during hyperventilation with so-called oxygen-enriched mixtures. In the study by Nunn and Payne and Nunn postoperative $P_aO_2$ varied between 39 and 82 mm. of mercury, hypoxemia being attributed to ventilation-perfusion abnormalities since chest films failed to reveal the presence of atelectasis. In the absence of $P_aO_2$ values while breathing 100 per cent $O_2$, it is not possible to exclude diffuse collapse as a contributing cause even if the roentgenogram.
fails to provide positive proof. Despite the consistent finding of postoperative hypoxemia, no cyanosis was evident, in these and other studies. Of the discrepancies in postoperative PaO₂ between the studies of Taylor, Scott and Donald on the one hand and those of Nunn and Payne and Conway and Payne on the other, will probably be resolved when the effects of controlled ventilation, use of muscle relaxants, extensive surgery and postoperative pain relieved by medication are all taken into account. Atelectasis and ventilation-perfusion abnormalities are not mutually exclusive phenomena. The degree to which each component contributes to abnormally low PaO₂ will depend on all of the aforementioned factors. Acute changes in the alveolar-arterial oxygen gradient during anesthesia (when ventilating with 95 per cent O₂ or higher and assuming insignificant changes in cardiac output) are most likely secondary to atelectasis, unrelated to airway obstruction, and need not be visible on roentgenograms. Acute collapse induced by blocking a bronchus is equally effective in producing a rise in venous admixture. Quantitation of changes in calculated shunt as related to the clinical changes associated with atelectasis, i.e., fever, tachypnea, altered breath sounds, roentgenogram patterns, etc., is badly needed, and several problems remain to be clarified before we can define precisely the causes of hypoxemia. The reader is particularly advised to note the normal PaCO₂ levels recorded by all these authors despite the marked lowering of the oxygen tension.

The practical value of monitoring the arterial P O₂ during thoracotomy is illustrated in figure 15. The low arterial oxygen tensions obtained when the patient was breathing essentially 99 per cent O₂ indicated a striking degree of venous admixture, suggestive of extensive collapse of functional airspaces. Auscultation of the right (lower) side of the chest revealed no gross changes (patient lying in the right lateral decubitus position); repeated suctioning of the tracheobronchial tree produced no improvement in the blood gas values. The chest film taken immediately postoperatively with the patient supine, revealed right lower lobe atelectasis. Craig, Bromley and Williams have described the relatively frequent occurrence of atelectasis in the dependent lobes during thoracotomy in the lateral decubitus position and its occurrence may easily escape detection by routine clinical examination.

Once atelectasis has occurred, the extent and success of functional re-expansion is probably related to the magnitude of the deep
breath and the duration of collapse. Björk and Hilty have shown that preoperative arterial oxygen tensions may not be restored until 2 weeks following thoracotomy for segmental or lobar resection. Other factors, including anemia, obesity, and prolonged bed rest are known to increase the alveolar-arterial O₂ gradient and will compound the iatrogenic changes introduced by anesthesia and surgery.

We know surprisingly little about what anesthetic agents do to the pulmonary distribution of gas and blood flow. The effect of various pharmacological agents on the sighing mechanism is yet to be defined. We do not know how breathing 100 per cent O₂ affects the normal sighing rate in adult, nonmedicated subjects and how such factors may play a role in the changes usually attributed to the breathing of high O₂ concentrations. Recently, it has been suggested that premedication of patients for operation with atropine results in a significant lowering of the arterial oxygen tension when compared to corresponding controls. These findings were not confirmed in a later study in 5 adult subjects.

Continuous intra-arterial recording of P₀₂ in dogs during the administration of norepinephrine has revealed changes consistent with diversion of blood away from well-ventilated areas. The effect of vasopressors on skin and muscle O₂ tension (implanted platinum electrodes) has been studied by Greene, Davies and Bell and by Willenkin and Greene. Simultaneous measurements of arterial P₀₂ in similar studies would indicate the extent to which the vasopressor acts directly on the pulmonary circulation and/or the blood supply to the end-organ. We have little information on the factors governing oxygen supply and blood flow to peripheral regions. However, there is reason to believe that oxygen tensions may take precedence over oxygen content in regulating the circulatory response to hypoxia.

When one considers the many factors known to influence the position of the dissociation curve, it is evident that a measurement of saturation alone cannot provide a rapid reference to the state of gas exchange in the lungs or the oxygen pressures supplied to the vital organs. It should be evident by now that standards of hypoxia may have to be reassessed and concepts of “safe” anesthesia when using oxygen-enriched mixtures re-evaluated. It is likely that cases of unexplained death during surgery and in the postoperative period are, and have been, secondary to unsuspected hypoxemia. As anesthesiologists, we carry the burden of proof when asserting that our patients are not hypoxic regardless of skin and blood color, vaso-motor reactions, inspired O₂ concentrations or oxyhemoglobin saturation levels.

Conclusions

The problem of adequate oxygenation in anesthesia has been reviewed in terms of the arterial oxygen tension, a parameter more sensitive and reliable than oxyhemoglobin saturation or oxygen content for defining incipient states of hypoxia. Evidence has been presented that ventilation standards based on arterial carbon dioxide tensions cannot be relied upon to insure integrity of pulmonary hemodynamics, or adequacy of oxygenation despite ventilation with O₂ concentrations that are higher than normal.

Assessment of the arterial oxygen tension in clinical anesthesia has been hampered in the past by a lack of appropriate measuring devices. However, technical advances of the past decade have overcome this difficulty. Criteria for ventilation based on the carbon dioxide tension must now find their counterpart in oxygenation. The future will probably provide techniques superior to the oxygen electrode, but this should not cloud the importance of acquiring a working knowledge of blood-gas exchange and a better understanding of the factors governing the uptake and distribution of O₂.

Available data on oxygenation in man can be summarized as follows:

1. General anesthesia is associated with an alteration in the pattern of ventilation which may result in significant atelectasis.

2. Abnormalities of the ventilation-perfusion ratios (which include atelectasis), lead to impaired oxygenation despite “adequate” ventilation as defined by normal arterial carbon dioxide tensions.

3. General anesthesia with “oxygen-enriched” mixtures does not insure against hy-
poxemia regardless of gas flow rates or breathing systems.

(4) Ventilation-perfusion abnormalities, including atelectasis, are invariably present in the postoperative period. Anesthesia, surgery, postoperative pain and medication disrupt the normal pattern of ventilation and promote pulmonary collapse. Atelectasis, secondary to small airway obstruction, is not the major problem in the postoperative patient.

(5) Hypoxemia §§ in the postoperative period is the rule in the patient breathing room air. The component contributed by atelectasis can be estimated by measuring arterial $P_{O_2}$ during ventilation with 100 per cent $O_2$.

(6) Postoperative hypoxemia cannot be recognized by the clinical signs usually described for this condition. Its importance to the welfare of the patient must be defined.

(7) Adequacy of pulmonary gas exchange can be assessed only by knowledge of both arterial blood $P_{O_2}$ and $P_{CO_2}$ levels.

§§ Hypoxemia is here defined as any lowering in arterial oxygen tension below the value found in the particular patient prior to elective surgery and in the absence of medication. Obviously, the physiological importance of these changes must be determined. Until this is done considerations of safety suggest that we make every attempt to maintain this level of oxygenation.

Appendix

Derivation of the Shunt Equation. The amount of oxygen taken up (ml./minute) during the passage of blood through the lungs equals the product of cardiac output ($Q_T$—in 1./minute) times the arterial $O_2$ content ($C_{O_2t}$—in ml./lt.). This represents the sum of 1. the shunt flow ($Q_S$) times the mixed venous content ($C_{O_2v}$), plus 2. the flow to ventilated alveoli ($Q_{Alveoli}$) times the $O_2$ content of pulmonary capillary blood after complete equilibration with alveolar $P_{Alveoli}$.

These considerations can be presented as follows:

$$Q_T C_{O_2t} = Q_S C_{O_2v} + Q_{Alveoli} C_{O_2Alveoli}$$

and

$$Q_T = Q_S + Q_{Alveoli}$$

Strictly speaking, the occurrence of ventilation-perfusion ratios deviating from the ideal requires that $Q_S C_{O_2v}$ be expressed as $Q_S C_{O_2v} + Q_S C_{O_2v} + Q_S C_{O_2v} + \ldots + Q_S C_{O_2v}$.

• The amount of recirculating arterial blood from the bronchial arteries to the pulmonary veins is negligible and may be disregarded.

• Except when hypoxic mixtures are administered diffusion does not impose any limitations on complete alveolar-capillary blood equilibration.

where the subscripted $Q$ and $C$ represent perfusion and $O_2$ content for the entire spectrum of ventilation-perfusion variations. This problem has been discussed by Finley.

Substituting from (2) into (1):

$$Q_T C_{O_2t} = Q_S C_{O_2v} + (Q_T - Q_S) C_{O_2Alveoli}$$

or

$$Q_T C_{O_2t} = Q_S C_{O_2v} - Q_S C_{O_2Alveoli} + Q_T C_{O_2Alveoli}$$

Equation (1) can be rearranged to the following:

$$Q_S C_{O_2v} - Q_S C_{O_2Alveoli} = Q_T (C_{O_2t} - C_{O_2v})$$

$$Q_T = \frac{C_{O_2v} - C_{O_2Alveoli}}{C_{O_2t} - C_{O_2v}}$$

Equation (7) represents the shunt equation. However, direct solution of this equation is not possible since pulmonary capillary blood cannot be sampled for the measurement of its $O_2$ content. When 100 per cent $O_2$ is breathed, and complete denitrogenation has been achieved, we may calculate the alveolar $O_2$ tension as follows:

$$P_{AO_2} = P_H - P_{H2O} - P_{CO_2}$$

where

$P_{H2O} = \text{water vapor pressure at temperature } T$

$P_{CO_2} = \text{arterial } CO_2 \text{ tension, assumed to equal the alveolar } CO_2 \text{ tension.}$

The error introduced by this assumption may produce a maximum error of 2 per cent in the calculated $P_{AO_2}$.

When the alveolar $P_{AO_2}$ is well above 200 mm. of mercury pulmonary capillary blood becomes fully saturated and the additional oxygen goes into solution in accordance to Henry's law:

$$C_{O_2} = \alpha T_{\text{blood}} \times \frac{1}{760} \times P_{AO_2}$$

The pulmonary capillary $O_2$ content ($C_{O_2}$) may be expressed as follows:

$$C_{O_2} (\text{vols. }%) = (Hg \times 1.34)$$

$$Q_t \text{ taken up by hemoglobin}$$

$$+ \left[ \frac{\alpha T_{\text{blood}} \times \frac{1}{760} \times P_{AO_2} \times 100}{O_2 \text{ in physical solution}} \right]$$

where

$Hg = \text{grams of hemoglobin}$

$\alpha T_{\text{blood}} = \text{Bunsen solubility coefficient of blood at temp. } T.$

$\frac{1}{760} = \text{factor used to correct the Bunsen solubility coefficient to milliliters taken up per mm. of mercury of gas pressure.}$
When the arterial $Q_r$-tension is above the value required for full saturation of hemoglobin then its $O_2$ content can be written:

$$C_{O_2}(\text{vols. }\% ) = \frac{(Hg \times 1.34)}{O_2 \text{ taken up by hemoglobin}} + \left(\frac{\sigma_{O_2}}{\sigma_{\text{blood}}} \times \frac{1}{760} \times P_{O_2} \times 100 \right). \quad (11)$$

Subtracting equation (11) from (10) we get:

$$C_{CO_2} - C_{O_2}(\text{vols. }\%) = \frac{\sigma_{O_2}}{\sigma_{\text{blood}}} \times \frac{100}{760} (P_{O_2} - P_{CO_2}). \quad (12)$$

The right hand side of equation (12) represents the amount by which mixed venous blood lowers pulmonary capillary $O_2$ in the presence of a shunt. At normal body temperature:

$$\frac{\sigma_{O_2}}{\sigma_{\text{blood}}} \times \frac{100}{760} = 0.0031 \quad (13)$$

from equation (12):

$$C_{CO_2} = C_{O_2} + 0.0031 (P_{O_2} - P_{CO_2}). \quad (14)$$

Substituting for $C_{CO_2}$ in equation (7):

$$\frac{Q_r}{\dot{Q}_r} = \frac{C_{CO_2} - C_{O_2}}{C_{CO_2} - C_{O_2}} = \frac{0.0031 (P_{O_2} - P_{CO_2})}{C_{CO_2} - C_{O_2}} = 0.0031 (P_{O_2} - P_{CO_2}). \quad (15)$$

Equation (15) is a modified form of the shunt equation applicable when 100 per cent $O_2$ is being breathed and with lower inspired concentrations only when $P_{CO_2}$ is above full saturation of hemoglobin.

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