Review Article

Measurement of Blood Oxygen Tension in Anesthesia

Myron B. Laver, M.D., and Astrid Seifen, M.D.

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, 42, 68, 120, 122, 123, 157, 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 O_2 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 dissolved 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

From the Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts. Portions of the work reported herein have been supported by Public Health Service grants HE 07432-01, HE 06848-03, HE 08558-01, HE 5859-04 and by Mallinckrodt Chemical Works.

* As defined in physical chemistry the oxygen electrode is a gas electrode used for *p*H measurements. To avoid the confused terminology Davies [47] has proposed the name oxygen cathode for the O_2 tension measuring device, a suggestion well worth adopting.

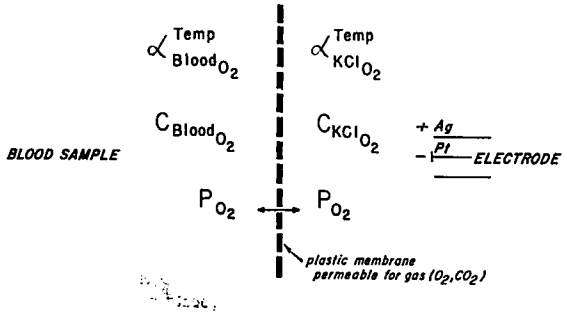


FIG. 1. Diagram indicating the principle underlying oxygen tension measurements with a membrane covered platinum electrode. $\alpha = O_2$ solubility coefficient; $C_{O_2} = O_2$ content $P_{O_2} = O_2$ tension.

1. The only parameter equilibrating across the membrane is P_{O_2}

2. The only parameter the electrode measures is $C_{KCl_{O_2}}$

tension of a gas to the number of its molecules in a particular solution is known as the Bunsen solubility coefficient (α), 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° 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:

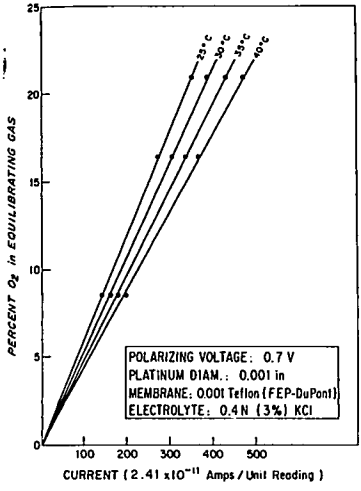
$$O_2 + 2H_2O + 2e^- \longrightarrow H_2O_2 + 2OH^- \quad (1)$$

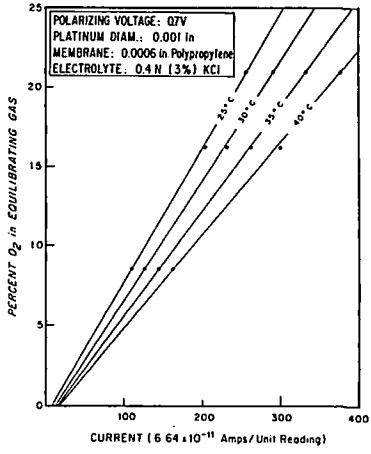
$$H_2O_2 + 2e^- \longrightarrow 2OH^- + 2H^+ \longrightarrow 2H_2O \quad (2)$$

These reactions are thought to be irreversible [86] 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.*[39] 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





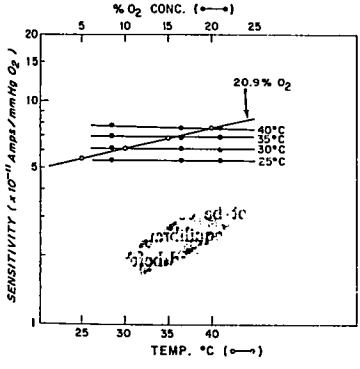


FIG. 2A.

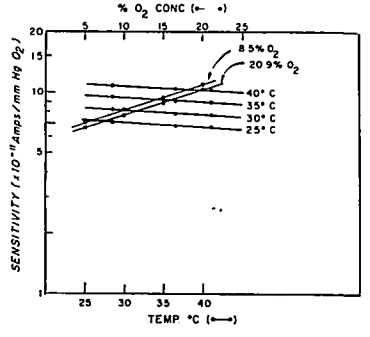


FIG. 2B.

FIG. 2. Effect of temperature on sensitivity (amperes/mm. 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-vivo* 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/mm. of mercury P_{O_2}) over the P_{O_2} range employed (O – 155 mm. 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.[34, 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} = partial pressure of O_2

α_{O_2} = O_2 solubility coefficient (Bunsen) of a particular fluid

V = 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:

$$O_2^T \text{ content} = \alpha^T_{O_2} \cdot V \cdot P_{O_{2G}} \cdot \frac{1}{760} \qquad (3)$$

where $P_{O_{2G}}$ is the partial pressure of oxygen of the equilibrating gas. If a sample of water equilibrated with $P_{O_{2G}}$ 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:

$$\underbrace{O_2^T \text{ content } (H_2O)}_{\substack{\text{content of sample} \\ \text{outside cuvette}}} = \Big[\underbrace{(\alpha^T_{O_{2H_2O}} \cdot V_{H_2O} \cdot P^T_{O_{2H_2O}})}_{\substack{O_2 \text{ content of sample} \\ \text{inside cuvette}}} + \underbrace{(\alpha^T_{O_{2KCl}} \cdot P^T_{O_{2H_2O}} \cdot V_{KCl})}_{O_2 \text{ content of electrolyte}} \Big] \times \frac{1}{760} \qquad (4)$$

The final oxygen tension in the cuvette ($P^T_{O_{2H_2O}}$) 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 microvolumes 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 [99] 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 [109] 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.[124] 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,[77] using Pflüger's method [124] reported a mean arterial oxygen tension of 78.7 mm. of mercury in dogs, while Fredericq [62] found this value to vary between 12 and 14 per cent of an atmosphere.

In 1898 Haldane [71] 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 [172] which has dominated the laboratory measurement of blood oxygen contents for almost half a century. However, for O_2 tensions above ambient air 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

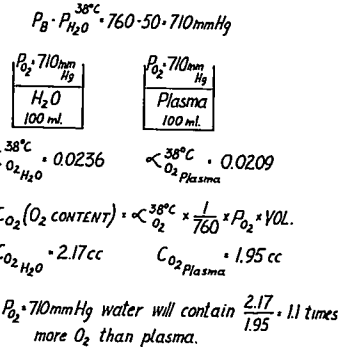


FIG. 3. O_2 content differences demonstrated in two solutions (water and plasma) having different O_2 solubility coefficients. At similar oxygen tensions water will contain 1.13 times (*i.e.*, $\alpha_{O_2 H_2O}^{38°C.} / \alpha_{O_2 Plasma}^{38°C.}$) more oxygen than plasma. Conversely, at similar O_2 contents, the partial pressure of oxygen in plasma will be 1.13 times higher than in water. A bare platinum electrode calibrated in water but immersed in plasma will not give the same reading for the oxygen tension (*i.e.*, when $P_{O_2} = 710$ mm. of mercury in both) due to differences in O_2 solubility coefficients and diffusion characteristics.

to hemoglobin. At partial pressures above full saturation of hemoglobin the changes between O_2 content and tension are related by the solubility coefficient (α) 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 (α) of plasma.

Danneel,[46] 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 [78] in 1925. Excepting the plateau, current changes in proportion to the voltage both below and above this region.

Berggren,[18] Wiesinger,[175] Baumberger,[13, 102] and Beecher, Follansbee, Murphy and Craig [14] 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 anaerobically separated plasma, not whole blood. Bartels [8] varied the applied voltage in order to maintain a constant current at all P_{O_2} 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.[11]

Use of stationary bare platinum electrodes in flowing liquids and biological media have been described in detail by several authors.[30, 32, 33, 116, 164] Morgan and Nahas [113] applied a fine film of silicone to the platinum surface of a rapidly rotating electrode (described earlier by Kolthoff and Laitinen [85]) in the hope of preventing deposition of the protein. Readings were reported to be related linearly to whole blood P_{O_2} in a range from 50 to 250 mm. of mercury but interference by changes in P_{CO_2} could not be eliminated. Drenckhahn [32] reported on the use of a collodion covered platinum wire (diam. 0.15 mm.) for measuring P_{O_2} in defibrinated whole blood. A satisfactory linear relationship was obtained over a P_{O_2} 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 [178] using a vibrating mercury electrode in a flow-through cuvette and an otherwise conventional polarograph, a system previously described by Clements and Moore.[40] 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,[134] 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, CO_2 and O_2 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_{O_2} levels could not be determined.

In 1953, Clark, Wolf, Granger and Taylor [39] 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 [156] was in fact based on the subsequent work of Clark.[38]

Severinghaus and Bradley [152] 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) Rooth, Sjöstedt and Caligara [135] (stainless steel blade) and Gleichmann and Lübbers [60] (glass coated iron rod). High speed rotation of the entire electrode was utilized by Kreuzer, Watson and Ball [90] 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 [127] 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 [45] reported their experience with an arrangement similar to that described by Bartels and Reinhardt.[12]

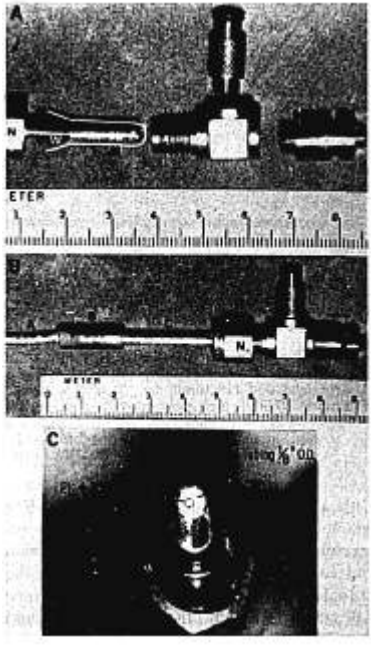


FIG. 4. *A:* Exploded view of electrode and flow-through cuvette. After dipping the electrode in 3 per cent KCl, the membrane (0.0006 inch polypropylene) is stretched over the electrode and held in place when the tapered washer (W) slides into position, as in *B*. Cuvette was made from a ⅛ inch T-tube 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. Charlton [36] 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

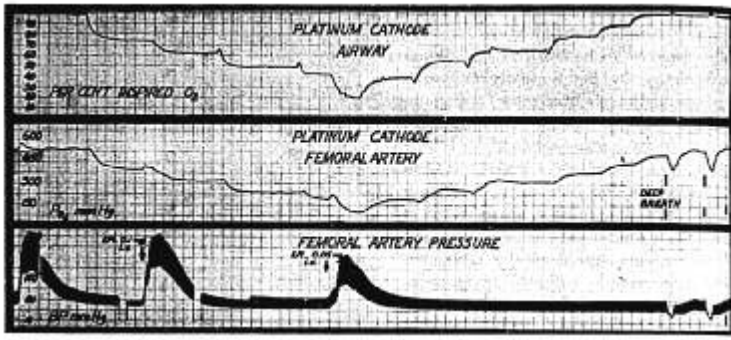


FIG. 5. Tracing of P_{O_2} obtained with one electrode (as in figure 4) mounted on the inspiratory limb of a piston pump respirator and another implanted in the femoral artery of an anesthetized dog (Platinum no. 20 B & S guage; silver tubing ⅛ inch (outside diameter); membrane: 0.0006 inch polypropylene; electrolyte: (0.4 *N*) KCl). Cuvette containing the electrode was buried subcutaneously in the groin to insure temperature compensation. Epinephrine was given to demonstrate the magnitude of the pressure artefact on the arterial P_{O_2} tracing. Note the effect of deep breaths at right on blood pressure and subsequent P_{O_2}.

with a thick membrane will give a reading which "represents O_2 tension far more accurately than O_2 concentration." O_2 tension and content will be related according to the O_2 solubility coefficient, while the membrane will affect primarily the O_2 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 O_2 consumption rate (small diameter platinum) and high O_2 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 Fatt [58] with the smallest platinum wire electrode (0.00004 inch, diameter) reported to date.

Thews [163] proposed a microtechnique for O_2 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 O_2 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 P_{O_2} 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 P_{O_2} 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 P_{O_2} values above 150 mm. of mercury were presented.

Systems permitting continuous measurement of O_2 tensions within a blood vessel or in a pump oxygenator have also been developed.

Krog and Johanson [91] mounted the platinum and silver elements at the tip of a cardiac catheter and used an appropriate polyethylene ring to secure the Teflon membrane in place.

Kreuzer, Harris and Nessler [88] 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_{O_2} readings. Montgomery, Paton, Lucero and Swan [110] 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 asepsis 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_2 electrode flow-through cuvette Meredith, Artesani and Mamlin [107] 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 [93] have utilized a solid electrode, patterned after the type designed by Glover,[67] and mounted in a flow-through cuvette that allowed continuous monitoring of arterial P_{O_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_{O_2} for a particular oxygen tension at various temperatures) can be defined when one is dealing with P_{O_2} values well above the full saturation of hemoglobin, *i.e.*, probably above P_{O_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_2 and current output, temperature being constant, implies that the sensitivity of the electrode (*i.e.*, amperes/mm. of mercury P_{O_2}) must remain constant over the full range of oxygen concentrations. Actual measurements of sensitivity between zero and 20.93 per cent O_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_2 is dependent on the so-called activation energy, or diffusion characteristics of the plastic membrane.[101] 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-vivo* electrode calibrated *in vitro*.

Reports with intravascular electrodes in man have been published by Said, David and Crosier [143] using a Beckman needle electrode (microelectrode); Koeff, Tsao, Vadnay, Wilson and Wilson [84] using an electrode designed by Tsao and Vadnay;[169] Charlton, Read and Read [37] using a needle electrode from the model originally designed by Charlton;[36] and Cosby *et al.*[43] with a Beckman microelectrode. Finley [60] has described an extra-vascular flow-through cuvette for measuring arterial P_{O_2} in man. Variations on these devices have been published by others.[108, 130, 155, 161] All suffer from the shortcoming that calibration *in vitro* with flowing samples of water or saline need not correspond to the response *in vivo*. Said, Davis and Crosier [143] 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 vivo* studies have indicated good agreement above P_{O_2} levels of 150 mm. of mercury.[93]

A recent review of oxygen electrodes not requiring polarization, (so-called galvanic cells) has been presented by Hobbs.[80] The reader interested in continuous measurement of airway O_2 concentrations will find that appropriate instruments have already been designed for this purpose.[80]

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 oxyhemoglobin 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, prerinsed 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, a cuffed endotracheal, or tracheostomy tube, preferably using a nonrebreathing 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.[3, 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 [53] 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 physical 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_{P_C}) was found to correlate well with rectal temperature (T_R) resulting in the following regression equation:

$$T_{P_C} = 37.15 + 2.4(T_R - 37.1) \qquad (5)$$

According to Afonso, Rowe, Castillo and Crumpton [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,[154] 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, Valasquez and Farhi [53] 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

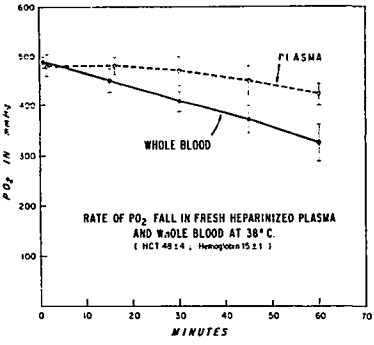


FIG. 6. Freshly drawn heparinized whole blood from normal adult subjects was tonometered at 38° C. with gas containing 70 per cent O_2, 5 per cent CO_2 and the balance N_2. P_{O_2} was measured at the end of tonometry and every 10 minutes thereafter, the blood being kept in the interim at 38° C. Plasma, obtained by centrifuging whole blood, was treated in a similar manner. Mean values ± S.D. of ten measurements.

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 *p*H 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.‖ 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

‡ Beckman macroelectrode manufactured by Backman Instruments, Inc., Fullerton, California.

§ Radiometer electrode available through London Co., Cleveland, Ohio.

‖ The purpose of the glass protrusion beyond the surface of the electrode is not clear. In fact we now make it standard practice to file the surface of newly purchased electrodes down until a perfectly flush surface is obtained. Although the sensitivity of the electrode is thereby increased, the advantage of greater stability and improved linear performance over a P_{O_2} range up to 1 atmosphere far outweighs this shortcoming.

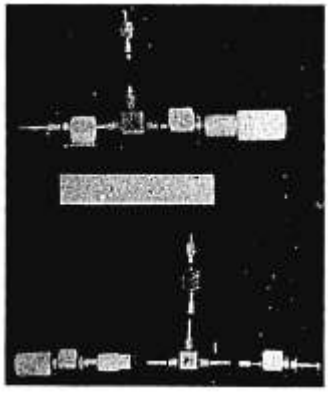


FIG. 7. Method utilized in our laboratory for mounting commercially available electrodes in brass or stainless steel cuvettes for *in-vivo* oxygen tension measurements. Entire assembly can be immersed in the water bath. Total volume of cuvette between the two female adaptors, with electrode in place: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

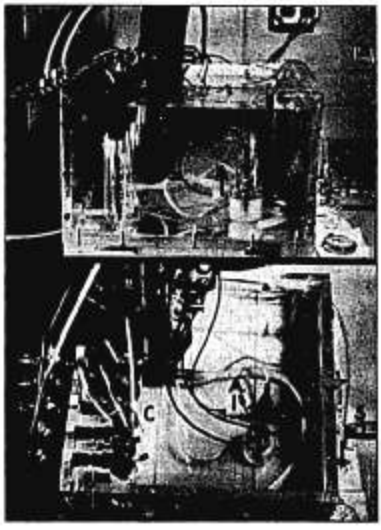


FIG. 8. Water bath containing a cuvette-mounted O_2 electrode and the test tubes used for equilibrating water with different O_2 concentrations. A = oxygen electrode mounted in cuvette. B = Severinghaus CO_2 electrode. C = test tubes containing water for equilibration with various O_2 concentrations. S = sample being introduced to O_2 cuvette. T = ¼ inch polyethylene cast tubing delivering O_2 gas mixtures.

per cent O_2). In our laboratories, where an average of 30 routine clinical P_{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 O_2: 20.9 per cent (compressed air) and 70 per cent. A third point of zero O_2 is established initially with a sodium sulfite in borax solution (sodium sulfite is a strong reducing substance at an alkaline *p*H), 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_{O_2} of subsequent samples. Consecutive readings at the high end of the curve (above 500 mm. of mercury P_{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.

McConn and Robinson,[104] using a commercial model of the electrode described by Bishop,[20] suggested a two-point method of calibration, one being defined as the electrode specific constant (K = current obtained from water equilibrated with air divided by the background current at zero O_2) and the second obtained with water equilibrated with air. These authors experienced difficulty with stable readings at high 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.

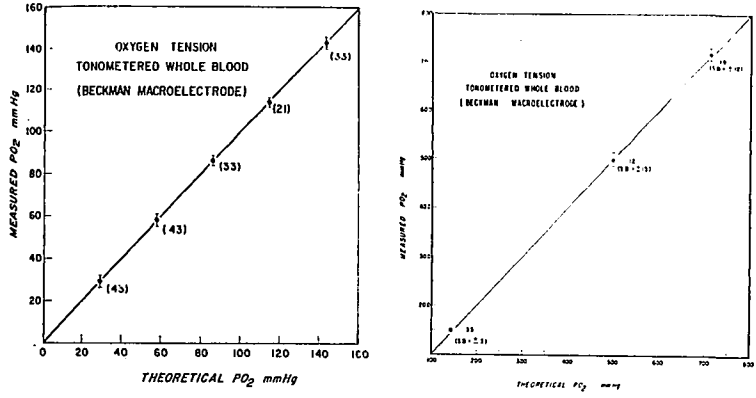


FIG. 9. Fresh heparinized whole blood was tonometered for 20 minutes, with different mixtures of oxygen, 5 per cent CO_2 and balance nitrogen. Calibration of the electrode was carried out with oxygen equilibrated water. Agreement between the theoretical (*i.e.*, P_{O_2} in gas phase determined by Scholander technique[145]) and measured blood oxygen tensions indicates the lack of difference between P_{O_2} measured in water and blood. This is a prerequisite for a properly functioning electrode system. Number of blood samples measured are indicated in parentheses.

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,[149, 152] we have found no differences in performance when using brass or stainless steel cuvettes except for the higher price of the latter. Perhaps, 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

Swagelok (R) fittings manufactured by Crawford Fitting Co., Cleveland, Ohio.

** Commercially available Teflon membranes are made by two different processes. DuPont Teflon FEP (fluoro-ethylene-propylene) (0.0005

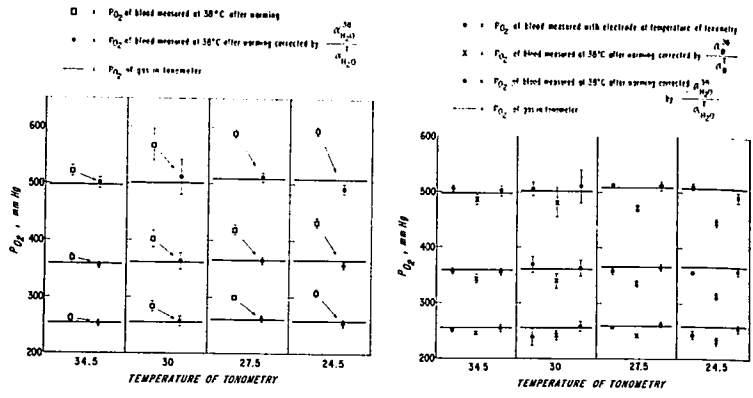


FIG. 10. Accuracy of temperature correction for whole blood assuming that blood has a constant relative solubility over the temperature range indicated (24.5° C. to 38° C.). (Relative O_2 solubility $= \frac{O_2 \text{ solubility in whole blood}}{O_2 \text{ solubility in water}}$). Blood was tonometered 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[115]. (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: 901, 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.[28, 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 [148] 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.[72] Data obtained with two oxygen electrodes maintained at 38° C. and a lower temperature supported Bohr's [20] 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

inch and 0.001 inch) is a thermoplastic resin made by melting the pure FEP for extrusion into a fine film; Dilectrix (Farmingdale, New York) Teflon TFE (tetra-fluoro-ethylene) (0.00025 inch) is a thermo-setting resin which cannot be melted, the films being formed by rapid cooling of the polymer. The thinnest FEP (0.0005 inch), appears to be more consistently free of minute perforations.

†† 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 [147] and recently reproduced in the "Handbook of Respiration." [50] 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 [143] 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.[72] The apparent discrepancies reported by Marshall and Gunning [103] with clinical measurements during hypothermia can probably be accounted for by the observations of Hedley-Whyte and Laver [72] (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.[137, 138] 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 very limited. Hopefully, future studies of oxygenation will correct this state of affairs.

TABLE I. Bunsen O_2 Solubility Coefficients (α) for Whole Blood (Data from the Literature)

Author	(α)	Temp. of Determination
Meyer[109]	0.018	20.7° C.
Bohr[26]	0.022	38° C.
Fasciolo & Chiodi[47]	0.0261	37° C.
Sendroy, Dillon & Van Slyke[147]	0.023	38° C.
Hüfner[81]	0.02486	38° C.

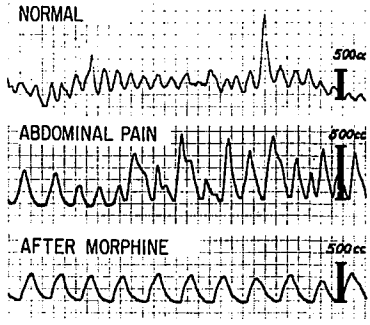


FIG. 11. The effect of morphine on tidal ventilation and sighing pattern in a subject with postoperative pain. Tracings obtained with pressure sensitive device placed around the patient's chest. Upstroke = inspiration. The single, large peak to the right in the uppermost channel represents a deep breath 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.)

Arterial oxygen tension changes during apnea following ventilation with room air or 100 per cent O_2 have been followed by Heller and Watson.[73, 74] 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 [105] 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 [17] 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.

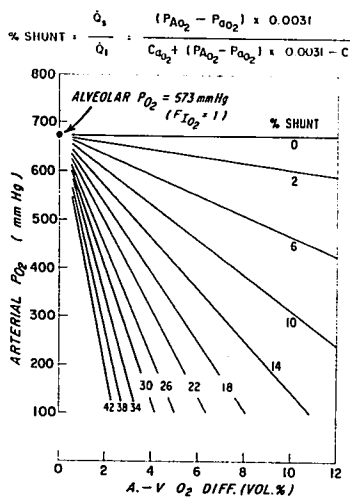


FIG. 12. Relation between Pa_{O_2}, A-V_{O_2} difference and shunt in percentage of cardiac output. Changes in the magnitude of the shunt and Pa_{O_2} can be appreciated by moving any arbitrary point either parallel to the A-V_{O_2} difference or arterial Pa_{O_2} lines. For explanation see text. (By permission from Laver, M. B., Morgan, J., Bendixen, H. H., and Radford, E. P., Jr.: Lung volume, compliance and arterial oxygen tensions during controlled ventilation, J. Appl. Physiol. 19, 725, 1964.)

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_{CO_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-aD_{O_2} [50, 93] when breathing 100 per cent O_2 points to progressive, diffuse atelectasis [16, 90, 105] as a cause of the difficulties. Narcotics in the postoperative period appear equally effective in reducing, or eliminating the normal sighing frequency,[54] thus perpetuating the low compliance state and the hypoxemia secondary to elevated A-D_{O_2} gradients (fig. 11).

Atelectasis and Alveolar-Arterial O_2 Gradients (A-aD_{O_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.[61] 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} ($P_{A_{O_2}}$) 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-V_{O_2} difference) and the percentage shunt, on the arterial O_2 tension.

Normal values for the A-aD_{O_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, 63, 106, 143] 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-aD_{O_2}) are invariably caused by alterations in the ventilation-perfusion ratio. Such disturbances are prominent in chronic obstructive emphysema [29, 60, 115] and mitral disease.[21, 51] A method for determining uneven pulmonary blood flow has recently been de-

scribed by Finley [60] and consists of continuous measurement of the arterial P_{O_2} from the moment that the subject begins to breathe 100 per cent O_2. The method is based on the principle "that the rate of rise of alveolar O_2 tension during oxygen inhalation depends on the distribution of inspired O_2 to well and poorly ventilated regions of the lung (in relation to their volume), while the rate of simultaneous rise of arterial O_2 tension depends on the distribution of pulmonary blood flow to these regions and the anatomical shunts." [60] 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 Uggla [25] have evaluated the arterial O_2 tension at rest and following standardized exercise (bicycle ergometer) as a test of pulmonary adequacy for withstanding extensive surgery. Exercise had little or no significant influence on arterial P_{O_2} in patients with low pulmonary reserve, a low P_{O_2} at rest being associated with a low P_{O_2} during effort. A positive correlation was found between maximum breathing capacity and resting P_{O_2} while patients with a high residual volume exhibited P_{O_2} levels significantly lower than normal.

Measurements of P_{O_2} in open chest dogs have demonstrated an essentially linear relationship between the A-aD_{O_2} and the calculated shunt.[70] Compliance does not appear as good an indicator of lung volume as the oxygen gradient during ventilation with 100 per cent O_2. Farhi and Velasquez [56] produced atelectasis in dogs by means of positive-negative 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 2. Alveolar-Arterial Oxygen Tension Gradients (A-aD_{O_2}) in Normal Subjects Breathing 100 Per Cent O_2 (Data from the literature)

Author	A−aD_{O_2}±S.D. (mm. Hg)	Method
Berggren[18]	11.3±1.5	Dropping mercury electrode
Morgan & Nahas[114]	57	Rotating platinum electrode
Wiesinger[175]	8±1.6	Dropping mercury electrode
Wilson *et al.*[173]	16±11	Dropping mercury electrode
Said & Banerjee[142]	26 (7–40)	Membrane covered platinum electrode
Cole & Bishop[41]	8.0 (20–29 yrs.) 21.3 (50–59 yrs.)	Membrane covered platinum electrode
Lillehei *et al.*[97]	44.4±19	Dropping mercury electrode
Polgar & Forster[127]	62.61±15.32	Membrane covered platinum electrode
Ayres, Criscitiello & Grabovsky[6]	37.1±24.5	Membrane covered platinum electrode
Fasciolo & Chiodi[57]	35.8±19.6	O_2 content of plasma
Wood[180]	40±53.2	O_2 content of plasma and blood
Nunn and Bergman[121]	14.8±55.2	Membrane covered platinum electrode

TABLE 3

Author	Age	Mean Pa_{O_2} (mm. Hg)	Method
Ulmer & Reichel[76]	Up to 30 30 to 40 40 to 50 50 to 60 Over 60	91 89 86 81 80	Membrane covered platinum electrode
Loew & Thews[97]	18 to 30 31 to 40 41 to 50 51 to 60 Over 60	93.7 81.5 80.1 76.9 70.0	Membrane covered platinum electrode
Riley *et al.*[132]	21 to 34	95.8	Bubble equilibration
Raine & Bishop[134]	Less than 40 More than 40	Sitting 97.6 Supine 95.3 Sitting 90.9 Supine 88.2	Membrane covered platinum electrode

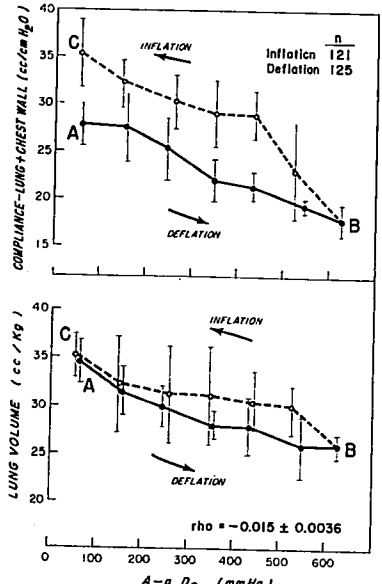


FIG. 13. The effect of repeated cycles of deflation (A to B) followed by repeated hyperinflations (B to C) on the relationship between lung plus chest wall compliance, or functional residual capacity, and the alveolar-arterial oxygen gradient. (By permission from Laver, M. B., Morgan, J., Bendixen, H. H., and Radford, E. P., Jr.: Lung volume, compliance and arterial oxygen tensions during controlled ventilation, J. Appl. Physiol. 19: 725, 1964.)

tional residual capacity, Laver, Morgan, Bendixen and Radford [90] demonstrated a close relationship between lung volume and A-aD_{O_2} during repeatedly induced collapse and expansion of dog lungs. Compliance appeared to follow the pattern previously described by Farhi and Velasquez [56] during collapse but returned toward normal values more readily than the A-aD_{O_2} following repeated deep breaths (see fig. 13). Atelectasis and an increased A-aD_{O_2} (when $F_{I_{O_2}} = 1$) can be produced experimentally by negative pressure respiration,[124, 142, 155] or direct aspiration of air from the airway.[90] The effects of thoracotomy on arterial O_2 saturation and tension have been studied by several investigators.[23, 27, 40, 82, 153]

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.[22]

The influence of altered end-expiratory resistance or pressure and various airway pressure patterns on the magnitude of the A-aD_{O_2} has been investigated by Frumin, Bergman, Holaday, Rackaw and Salanitre [64] and more recently by Bergman,[19] during short-term studies in man and dogs. Hill, Finley, Takamura, Orallo and Bonica,[79] 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 [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.[4, 31, 174] Sackur [140] 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.[61, 131]

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.[65] 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.[61, 63, 106, 179]

Atelectasis and Ventilation-Perfusion Abnormalities. Maldistribution between ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$),[29, 126] also contributes to the alveolar-arterial oxygen difference when breathing room air [6, 55, 90, 95] 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 $A\text{-}aD_{O_2}$ can be defined by measuring the arterial oxygen tension when ventilating with 100 per cent O_2.‡‡ 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) 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 [129] and Riley and Cournand.[131, 132] 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 $A\text{-}aD_{O_2}$ gradients,[15, 16, 73] we note that in the presence of a normal cardiac output ($A\text{-}V_{O_2}$ difference = 5 to 6 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]

‡‡ This critical difference is often overlooked by clinicians evaluating ventilation during anesthesia and surgery. When breathing 100 per cent O_2 and after adequate denitrogenation, the effect of ($\dot{V}_A/\dot{Q}$) abnormalities are eliminated and the $A\text{-}aD_{O_2}$, above the value resulting from anatomic right to left shunts, is due to atelectasis alone. The closer the inspired O_2 concentration moves from 100 per cent to that in room air, the greater will be the contribution of ventilation-perfusion abnormalities to the $A\text{-}aD_{O_2}$. This arises from the unequal removal or addition of nitrogen to the various gas spaces. The resulting nitrogen gradient therefore must coincide with a change in $A\text{-}aD_{O_2}$.

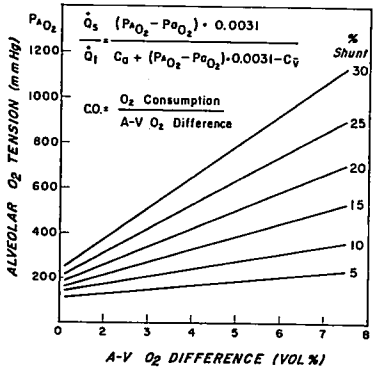


FIG. 14. Iso-shunt lines indicating the required alveolar oxygen tension ($P_{A_{O_2}}$) necessary to maintain an arterial oxygen tension (Pa_{O_2}) of 100 mm. of mercury at various A-V_{O_2} differences. It can be seen that in the presence of a shunt equal to 10–15 per cent of cardiac output and a normal cardiac output (A-V_{O_2} difference = 5 to 6 volumes per cent) a minimum of 50 per cent O_2 is required in the inspired air to maintain the appropriate arterial O_2 tension. Ventilation with other mixtures, such as nitrous oxide-oxygen in a ratio of 2:1 must result in arterial P_{O_2} values well below 100 mm. of mercury despite a minimal shunt. An increase in cardiac output (*i.e.*, A-V_{O_2} difference moving to the left) will drop the $P_{A_{O_2}}$ further. These considerations do not take into account the venous admixture effect which becomes prominent when less than 100 per cent O_2 is being used and which will become superimposed on the effects illustrated by the graph and cause an additional lowering of the arterial O_2 tension.

Gordh, Linderholm and Norlander [68] were the first to utilize the oxygen electrode for assessing the intra and postoperative arterial oxygen tension levels resulting from various modes of anesthesia. These authors reported a significant rise in the alveolar-arterial oxygen gradient in patients breathing room air 24 hours following either spinal or barbiturate-nitrous oxide-succinylcholine anesthesia, while patients receiving ether exhibited a considerably lesser change. The altered gradients were attributed primarily to atelectasis, present 24 hours after anesthesia and surgery, with very few patients being noted to have had clinical signs of pulmonary complications. Palmer and Gardiner [123] presented data on postoperative arterial oxygen tensions following partial gastrectomy. In 14 patients without evidence of atelectasis (method of establishing this was not defined by the authors) the mean Pa_{O_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 Pa_{O_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 [162] studied the arterial oxygen tensions of 6 patients undergoing uterine curettage under halothane-oxygen and spontaneous respiration. In the course of anesthesia the Pa_{O_2} varied from 332.8 ± 72.75 to 380.5 ± 107.98 mm. of mercury. This value agrees with the data of Bendixen, Hedley-Whyte and Laver,[16] suggesting that atelectasis was present at the time of sampling (breathing a minimum of 95 per cent O_2 should result in a Pa_{O_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 intermittant deep breathing, one cannot be too surprised at the normal postoperative Pa_{O_2} values. In the study of Conway and Payne [42] 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 [42] reported a mean Pa_{O_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 [122] and Nunn,[120] postoperative Pa_{O_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 Pa_{O_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.[168] The discrepancies in postoperative Pa_{O_2} between the studies of Taylor, Scott and Donald [102] on the one hand and those of Nunn and Payne [122] and Conway and Payne [42] 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 Pa_{O_2} will depend on all of the aforementioned factors.

Acute changes in the alveolar-arterial oxygen gradient during anesthesia (when ventilating with 95 per cent O_2 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.[111, 112] 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 P_{CO_2} levels recorded by all these authors despite the marked lowering of the oxygen tension.

The practical value of monitoring the arterial P_{O_2} during thoracotomy is illustrated in figure 15. The low arterial oxygen tensions obtained when the patient was breathing essentially 99 per cent O_2 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 [44] have described the

Pt MB 9 OPEN REPAIR MITRAL STENOSIS		Pa_{O_2} mm Hg	Pa_{CO_2} mm Hg	pH
CONTROL ROOM AIR		56	46	7.40
CHEST CLOSED	O_2 + HALOTHANE	205	36	7.48
	$N_2O + O_2$ 2.5L + 2.5L	43	26	7.57
CHEST OPEN	O_2 + HALOTHANE	45	34	7.50
	$N_2O + O_2$ 2.5L + 2.5L	20	40	7.46
POST-PUMP LUNGS EXPANDED	O_2 + HALOTHANE	55	25	7.56
	$N_2O + O_2$ 2.5L + 2.5L	56	26	7.56
RECOVERY ROOM	ROOM AIR	58	44	7.38
	O_2 BY MASK 10 L/MIN.	178	30	7.39

FIG. 15. Early detection of lobar atelectasis by determination of arterial oxygen tensions during operation. Ventilation with halothane-oxygen or 50 per cent O_2–50 per cent N_2O. Patient was a 51 year old woman who had an open repair of mitral stenosis with the aid of a pump oxygenator. Right lateral decubitus position. *Upper right:* chest roentgenogram taken after vigorous chest physiotherapy combined with multiple and repeated deep breaths administered manually via a tight fitting face mask. Table indicates blood gases determined during surgery. Note that arterial P_{O_2} breathing room air (taken at the time of the chest film on the left) was not different from the control value obtained preoperatively. (Courtesy of Dr. Phillips G. Hallowell.)

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.[93] Björk and Hilty [23] 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,[130] obesity,[141] and prolonged bed rest [18] are known to increase the alveolar-arterial O_2 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,[54] is yet to be defined. We do not know how breathing 100 per cent O_2 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 O_2 concentrations.[167] 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.[165] These findings were not confirmed in a later study in 5 adult subjects.[121]

Continuous intra-arterial recording of P_{O_2} in dogs during the administration of norepinephrine has revealed changes consistent with diversion of blood away from well-ventilated areas.[87] The effect of vasopressors on skin and muscle O_2 tension (implanted platinum electrodes) has been studied by Greene, Davies and Bell [69] and by Willenkin and Greene.[176] Simultaneous measurements of arterial P_{O_2} in similar studies would indicate the extent to which the vasopressor acts directly on the pulmonary circulation [118] 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.[173] However, there is reason to believe that oxygen tensions may take precedence over oxygen content in regulating the circulatory response to hypoxia.[2]

When one considers the many factors known to influence the position of the dissociation curve,[7, 9, 84, 137, 171] 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, vasomotor reactions, inspired O_2 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 O_2 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 O_2.

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 ($\dot{Q}_T$—in l./minute) times the arterial O_2 content (C_{aO_2}—in ml./l.).* This represents the sum of 1. the shunt flow ($\dot{Q}_S$) times the mixed venous content ($C\bar{v}_{O_2}$), plus 2. the flow to ventilated alveoli ($\dot{Q}_{C_{O_2}}$) times the O_2 content of pulmonary capillary blood after complete equilibration with alveolar P_{O_2}.†

These considerations can be presented as follows:

$$\dot{Q}_T C_{aO_2} = \dot{Q}_S C\bar{v}_{O_2} + \dot{Q}_C C_{CO_2} \quad (1)$$

and

$$\dot{Q}_T = \dot{Q}_S + \dot{Q}_C \quad (2)$$

Strictly speaking, the occurrence of ventilation-perfusion ratios deviating from the ideal requires that $\dot{Q}_C C_{C_{O_2}}$ be expressed as $\dot{Q}_1C_1+\dot{Q}_2C_2+\dot{Q}_3C_3\cdots+\dot{Q}_nC_n$

* 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.[60]

Substituting from (2) into (1):

$$\dot{Q}_T C_{aO_2} = \dot{Q}_S C\bar{v}_{O_2} + (\dot{Q}_T - \dot{Q}_S) C_{CO_2} \quad (3)$$

or

$$\dot{Q}_T C_{aO_2} = \dot{Q}_S C\bar{v}_{O_2} - \dot{Q}_S C_{CO_2} + \dot{Q}_T C_{CO_2}. \quad (4)$$

Equation (4) can be rearranged to the following:

$$\dot{Q}_S C_{CO_2} - \dot{Q}_S C\bar{v}_{O_2} = \dot{Q}_T C_{CO_2} - \dot{Q}_T C_{aO_2}, \quad (5)$$

$$\dot{Q}_S (C_{CO_2} - C\bar{v}_{O_2}) = \dot{Q}_T (C_{CO_2} - C_{aO_2}), \quad (6)$$

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_{CO_2} - C_{aO_2}}{C_{CO_2} - C\bar{v}_{O_2}}. \quad (7)$$

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:

$$P_{A_{O_2}} = P_B - P^T_{H_2O} - P_{aCO_2}, \quad (8)$$

where

$P^T_{H_2O}$ = water vapor pressure at temperature T

P_{aCO_2} = arterial CO_2 tension, assumed to equal the alveolar CO_2 tension.

The error introduced by this assumption may produce a maximum error of 2 per cent in the calculated $P_{A_{O_2}}$.

When the *alveolar* P_{O_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:

$$C_{O_2} = \alpha^T{}_{O_{2Blood}} \times \frac{1}{760} \times P_{O_2}. \quad (9)$$

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

$$C_{C_{O_2}}(\text{vols. \%}) = \underbrace{(\text{Hg} \times 1.34)}_{\substack{O_2 \text{ taken up by} \\ \text{hemoglobin}}} + \underbrace{\left(\alpha^T{}_{O_{2Blood}} \times \frac{1}{760} \times P_{A_{O_2}} \times 100\right)}_{O_2 \text{ in physical solution}}, \quad (10)$$

where

Hg = grams of hemoglobin

$\alpha^T{}_{O_{2Blood}}$ = Bunsen solubility coefficient of blood at temp. T.

$\frac{1}{760}$ = factor used to correct the Bunsen solubility coefficient to milliliters taken up per mm. of mercury of gas pressure.

When the *arterial* O_2-tension is above the value required for full saturation of hemoglobin then its O_2 content can be written:

$$C_{aO_2}(\text{vols. \%}) = \underbrace{(\text{Hg} \times 1.34)}_{\substack{O_2 \text{ taken up by} \\ \text{hemoglobin}}} + \underbrace{\left(\alpha^{T}_{O_{2Blood}} \times \frac{1}{760} \times P_{aO_2} \times 100\right)}_{O_2 \text{ in physical solution}}. \quad (11)$$

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

$$C_{cO_2} - C_{aO_2}(\text{vols. \%}) = \alpha^{T}_{O_{2Blood}} \times \frac{100}{760}(P_{AO_2} - P_{aO_2}). \quad (12)$$

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:

$$\alpha^{T}_{O_{2Blood}} \times \frac{100}{760} = 0.0031 \quad (13)$$

from equation (12):

$$C_{cO_2} = C_{aO_2} + 0.0031(P_{AO_2} - P_{aO_2}). \quad (14)$$

Substituting for C_{cO_2} in equation (7):

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{0.0031(P_{AO_2} - P_{aO_2})}{C_{aO_2} - C_{\bar{v}O_2} + 0.0031(P_{AO_2} - P_{aO_2})}. \quad (15)$$

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_{aO_2} is above full saturation of hemoglobin.

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