APPLICATION OF PULSE OXIMETRY IN NEONATAL MEDICINE

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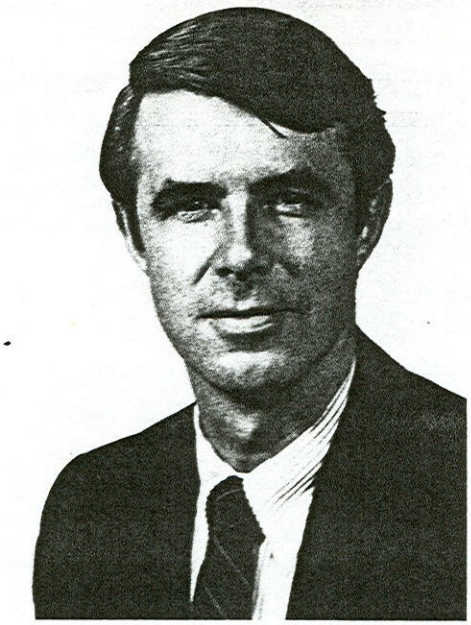

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Biographical Details

Dr. Hay is currently Associate Professor of Pediatrics and Head, Section of Neonatology, at the University of Colorado School of Medicine. He also serves as Director of the Neonatal Clinical Research Center and is Vice-Chairman of the Human Subjects Committee (Human Research Review Board) for the University of Colorado Health Sciences Center.

Dr. Hay received his bachelor's degree from Dartmouth College and his doctor of medicine degree from Yale University. He trained in Pediatrics at the University of Colorado Health Sciences Center and completed his clinical and research training in Neonatal-Perinatal Medicine in the Division of Perinatal Medicine at the University of Colorado Health Sciences Center.

In addition to his clinical and teaching duties in the Newborn and Intensive Care Nurseries at University Hospital, and his administrative duties, Dr. Hay has pursued research in fetal, placental and maternal metabolism during pregnancy and in neonatal nutrition. He has received several federal research grants and has published numerous research papers and review articles.

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Application of Pulse Oximetry in Neonatal Medicine

Introduction

The purposes of this monograph are threefold: 1) to describe the principles governing the transport of oxygen in blood, 2) to discuss the principles of *in vitro* (on blood samples) and *in vivo* (non-invasive) measurement of blood oxygen saturation and blood oxygen partial pressure, and 3) to compare the practical application of a pulse oximeter (the Ohmeda Biox 3700 Pulse Oximeter) to clinical measurements of blood oxygen saturation in preterm and term human infants. The practical application studies were performed by William W. Hay, Jr., M.D., Mario Eyzaquirre, M.D., and Julie Brockway under the auspices of the Pediatric Clinical Research Center in the Newborn Intensive Care Unit at University Hospital, University of Colorado Health Sciences Center, Denver, Colorado.

Transport of Oxygen in Blood: General Principles

Oxygen is transported in blood in two physical forms: 1) freely dissolved in the plasma water, and 2) bound reversibly to hemoglobin within the red blood cells *(1)*. Together these two forms of blood oxygen make up the "blood oxygen content."

The amount of oxygen dissolved in the plasma water is directly related to the partial pressure of oxygen in blood according to equation #1:

1. O_2 *dissolved* $= aPO_2$ *(mmHg)*

where "a" is the "solubility constant" for oxygen in blood and is equal to 23.0 ml of oxygen per liter of blood per atmosphere of oxygen at 38°C. PO_2 is the fraction of oxygen in the dry gas (0.2093) times the pressure of the dry gas (0.2093 x [760-47] mmHg). At normal sea level conditions the amount of oxygen dissolved in blood *(equation #2)* is about 4.5 ml/liter (0.2 millimoles/liter) and accounts for only about 2% of total blood oxygen content.

2. $[(23\ ml\ O_2/L)\ (0.2093)\ (760\text{-}47\ mmHg)] / 760\ mmHg = 4.5\ ml/L$

The largest portion (98%) of blood oxygen content is the oxygen bound to hemoglobin. The amount of oxygen bound to hemoglobin also is directly related to the partial pressure of dissolved oxygen in the blood. Under this pressure, oxygen diffuses into the red blood cells where it reacts with hemoglobin to form a chemical compound according to the equation:

3. $4\ O_2 + Hb = Hb\ (O_2)_4$

When fully saturated (combined) with oxygen, 1 gram of hemoglobin carries 1.34 ml of oxygen. Thus, for a normal newborn infant with 20 grams of Hb per 100 ml of blood (20% or 200 g/liter), hemoglobin would carry 268 ml of O_2 per liter, which can be compared with the much smaller amount (4.5 ml/liter) of oxygen dissolved in the plasma water. Thus, the amount of oxygen carried in blood is primarily dependent on the partial pressure of oxygen in blood (the PO_2) and the amount of hemoglobin in blood.

The relationship between blood partial pressure of oxygen and the amount of oxygen bound to hemoglobin is commonly expressed as "oxygen-hemoglobin affinity" and graphically presented *(Fig. 1)* as the percent of hemoglobin fully saturated with oxygen ($HbO_2/Hb + HbO_2$) x 100 related to the blood PO_2. Hemoglobin-oxygen affinity is modified by four factors *(Fig. 2)*: 1) hydrogen ion concentration ([H +]); 2) PCO_2; 3) temperature; and, 4) 2,3-diphosphoglycerate (2,3-DPG) concentration. Increased values of these factors act to decrease hemoglobin-oxygen affinity. For example, increased values for [H +], PCO_2 and temperature occur in the tissues at sites of active metabolism and thus aid in releasing O_2 from Hb, raising the local PO_2, making oxygen more available for tissue uptake. These conditions are reversed in the lungs where Hb uptake of O_2 is more important.

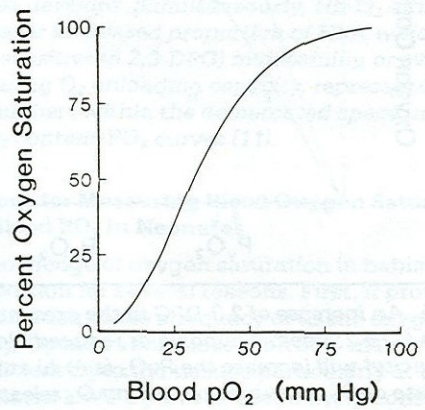


Fig. 1. *Oxygen–hemoglobin affinity curve of normal adult human blood (4 O_2 + Hb = Hb $(O_2)_4$) (1).*

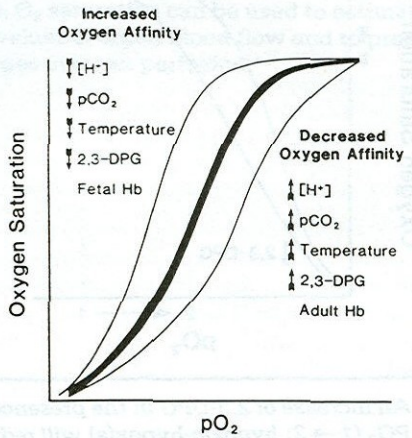


Fig. 2. *Factors affecting oxygen–hemoglobin affinity.*

2,3-DPG is produced as a by-product of glucose metabolism (glycolysis) *(4)*. Increased 2,3-DPG production occurs in response to chronically reduced tissue oxygen delivery, for example, with anemia *(5)*. In this situation *(Fig. 3A)* arterial PO_2 and oxygen saturation are normal but oxygen extraction (the amount of oxygen removed per volume of blood) is increased, resulting in a fall in venous PO_2 and saturation. The decreased Hb-O_2 affinity produced by the increased 2,3-DPG allows oxygen extraction to occur while preventing a further fall in venous PO_2. However, with chronic hypoxic-hypoxia (low PO_2, low O_2 saturation), an increased 2,3-DPG concentration would produce a disadvantage to oxygen transport by reducing blood oxygen carrying capacity (maximum arterial oxygen saturation and content) *(Fig. 3B)*.

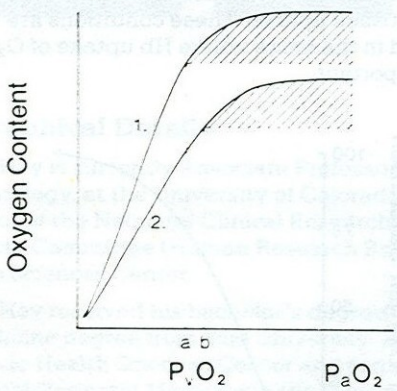


Fig. 3A. *An increase of 2,3-DPG in the presence of anemia (1 → 2; anemic hypoxia or reduced blood O_2 capacity) will increase the PvO_2 (a → b) at the same rate of O_2 consumption, aiding O_2 release to the tissues.*

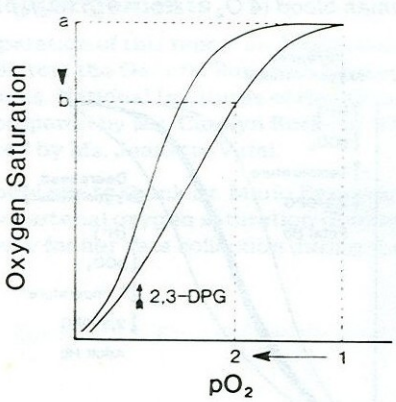


Fig. 3B. *An increase of 2,3-DPG in the presence of lowered PO_2 (1 → 2; hypoxic-hypoxia) will reduce arterial O_2 saturation (a → b) and thus O_2 delivery to the tissues.*

Oxygen Transport: Fetus

In fact, chronic hypoxic conditions (low PO_2) are handled with increased Hb-O_2 affinity in a large variety of biological situations, for example, in deep dwelling-fish versus surface-dwelling fish, tadpoles ("water breathers") versus frogs ("air breathers"), and the fetus versus adult *(6)*. In these conditions, the hemoglobin structure is altered such that Hb affinity for O_2 is increased resulting in higher O_2 saturation and blood O_2 content at relatively lower PO_2 values. In the fetus, the higher Hb-O_2 affinity is produced by a relatively decreased response of fetal hemoglobin (HbF) to 2,3-DPG *(7,8)*. This condition is important to the fetus because umbilical venous PO_2 (the oxygenated blood supply to the fetus) is limited by the uterine venous PO_2 (about 35-40 mmHg in human) *(9)*. At this low PO_2, increased Hb-O_2 affinity is essential to provide the fetus with an adequate oxygen supply *(Fig. 4)*.

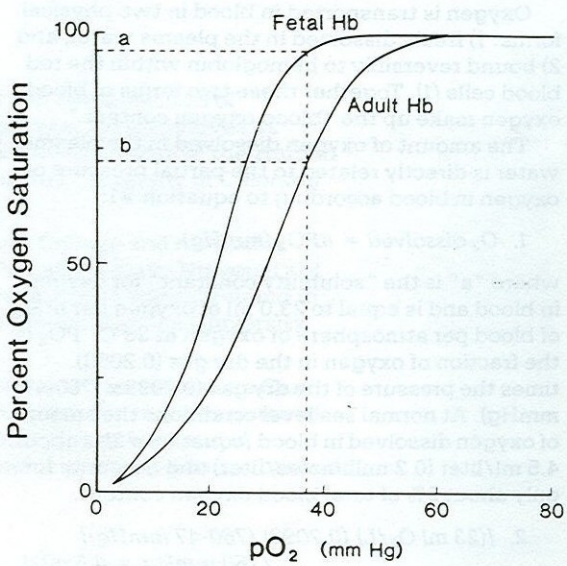


Fig. 4. *At the normal umbilical venous PO_2 (about 40 mmHg) increased O_2 affinity of HbF confers an O_2 carrying capacity advantage (a) relative to HbA (b) (5,6,7).*

Oxygen Transport: Neonatal

In the first hours following birth, the human infant is usually capable of raising its PO_2 to the normal adult level. However, because of the relatively high Hb-O_2 affinity of the HbF (still greater than about 80% of total Hb at term), the infant's blood will remain highly saturated (greater than 85%) even with PO_2's as low as 35-40 mmHg. As a result, these infants can look "pink" at very low PO_2's *(10)*. Thus a visual interpretation of "normal oxygenation" in newborn infants must be made with caution.

Over the first few weeks following birth, HbA production gradually replaces HbF with HbA *(11)*. The increased HbA concentration relative to HbF develops in response to the higher PO_2 in the infant's blood as a result of breathing air (or oxygen-enriched air), or may develop as a result of transfusions with adult donor blood. As a result, Hb-O_2 affinity decreases progressively due to the greater effect of 2,3-DPG on HbA compared with HbF *(Fig. 5A)*. The decreased Hb-O_2 affinity has an advantage of maintaining high capillary-venous PO_2 levels for a given O_2 extraction by the tissues, thereby increasing the efficiency of O_2 delivery. This decreased affinity becomes even more important in relation to the postnatal decrease of blood oxygen content due to the development of "physiologic" anemia *(Fig. 5B)*. Thus, the simultaneous reduction of Hb-O_2 affinity has the additional value of increasing O_2 unloading capacity as O_2 content falls, maintaining O_2 delivery to the tissues without requiring a decrease in capillary venous PO_2 *(11)*.

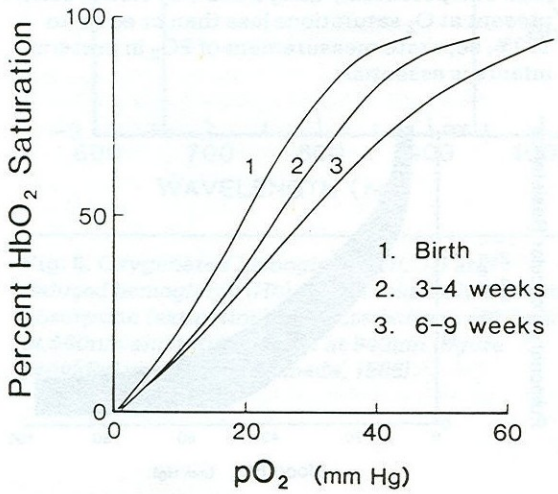


Fig. 5A. *Following birth, Hb-O_2 affinity decreases as HbA, which is more responsive to 2,3-DPG, replaces HbF (11).*

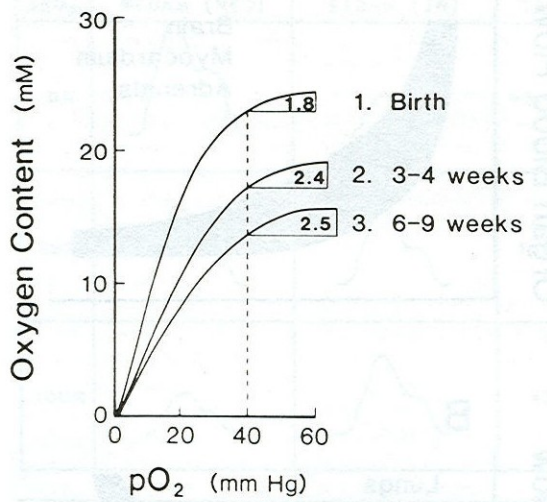


Fig. 5B. *Following birth, Hb-O_2 content falls as anemia develops. Simultaneously, Hb-O_2 affinity decreases (increased proportion of HbA which is more sensitive to 2,3-DPG) maintaining or even increasing O_2 unloading capacity, represented by the numbers within the demarcated space under the O_2 content-PO_2 curves (11).*

Reasons for Measuring Blood Oxygen Saturation and Blood PO_2 in Neonates

Knowledge of oxygen saturation in babies is important for several reasons. First, it provides an indication of the adequacy of tissue oxygen supply. O_2 saturations less than 80% may provide insufficient O_2 to the tissues particularly at the associated low PO_2 levels. Secondly, at constant Hb concentration, blood flow to the vital organs (brain and heart) is inversely related to blood O_2 saturation and directly related to O_2 saturation in other tissues (muscle, skin, gut) *(Fig. 6) (12,13)*. Thus, O_2 saturation can be used to estimate absolute values of organ blood flow and to predict changes in organ perfusion.

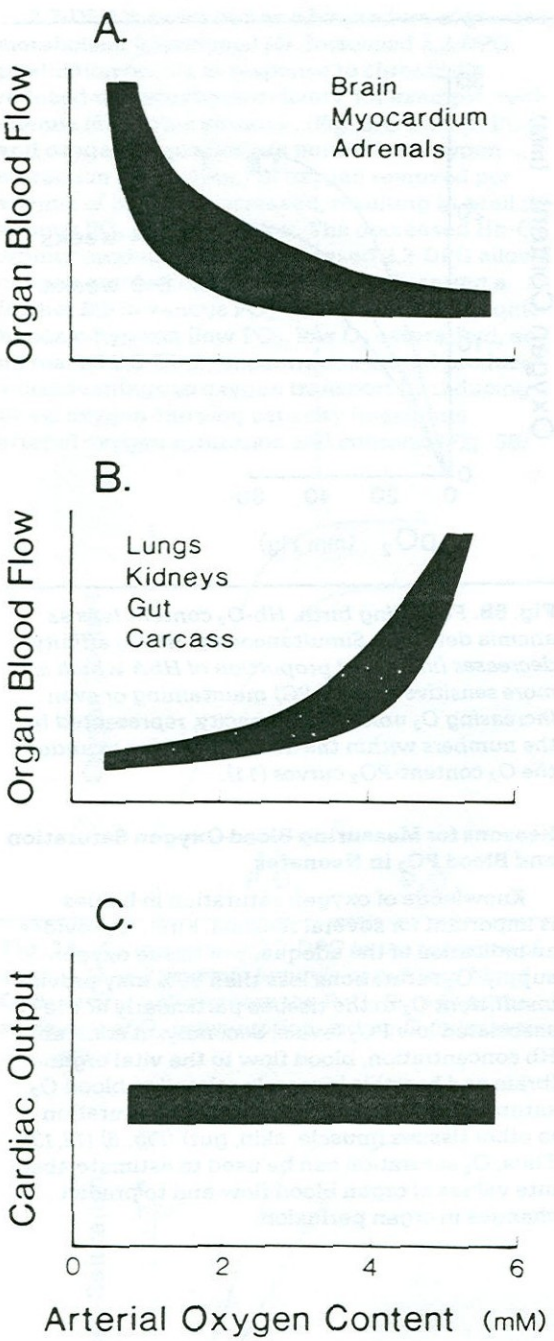


Fig. 6. *Redistribution of organ blood flow as blood O_2 content changes. (Taken from studies in late gestation fetal lambs) (12,13).*

Knowledge of blood PO_2 is also important. The pulmonary circulation and the diameter of the ductus arteriosus are both directly related to PO_2 specifically rather than to O_2 content as is the case with other tissues *(14)*. A high PO_2 dilates pulmonary arteries but constricts the ductus arteriosus *(Fig. 7)*. The mechanism(s) for these effects are not completely understood. The PO_2 effect on the pulmonary vasculature appears to be direct while the effect on the ductus arteriosus may be both direct and mediated by vasoactive substances (e.g., the arachidonic acid derivatives). Also, very high PO_2's are associated with oxygen free radical production which may lead to cellular and tissue injury *(15)*. The most common example of this process is believed to occur in preterm infants with immature retinal vascularization in whom hyperoxia has been associated with damage to the retinal capillary endothelium resulting in retrolental fibroplasia *(16)* (although vascular immaturity, choroidal blood flow, hypoxemia, and many other factors *(17)* are now considered as, or more important than PO_2 with respect to the etiology of retrolental fibroplasia). Because very high and potentially dangerous PO_2 values can be present at O_2 saturations less than or equal to 100%, separate measurement of PO_2 in preterm infants is essential.

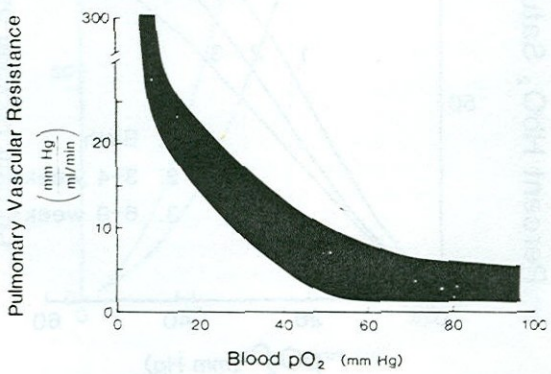


Fig. 7. *In contrast to other organs, pulmonary vascular resistance (and thus pulmonary blood flow) is PO_2 dependent (14).*

In Vivo Measurement of Blood Oxygen Saturation

In vivo, non-invasive O_2 saturation relies on the measurement of absorption of specific wavelengths of light by Hb and HbO_2 as they pass through tissue and blood *(18,19) (Fig. 8)*. In order to measure "arterial" O_2 saturation *(Fig. 9)*, measurements are recorded with reference to the change in light transmittance that occurs with each arterial pulse of blood flowing through the tissue *(Figs. 10,11)*. Thus, these instruments are called pulse oximeters. Since the ratio of transmittance at each of the two wavelengths (660 nm or Red; and 940 nm or InfraRed) varies according to

the percent oxygen saturation of hemoglobin, *(Fig. 10)*, the instrument can be programmed to calculate and display percent oxygen saturation during each pulse *(Fig. 11)*.

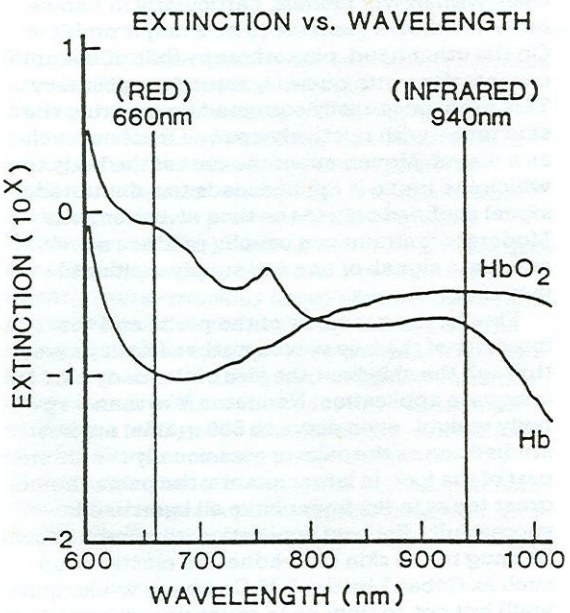


Fig. 8. *Oxygenated hemoglobin (HbO_2) and reduced hemoglobin (Hb) exhibit markedly different absorption (extinction) characteristics to red light at 660nm and infrared light at 940nm (figure provided courtesy of Ohmeda, 1986).*

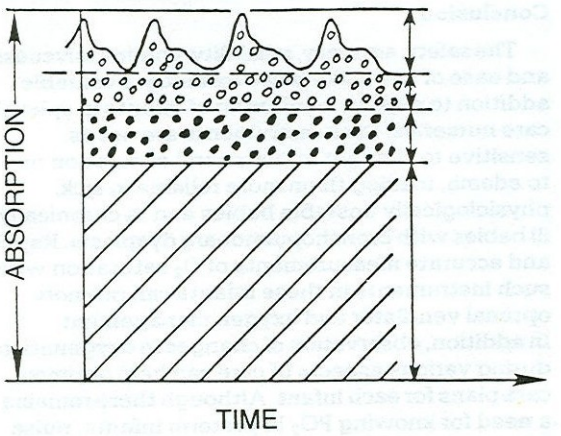


Fig. 9. *Absorption of light transmitted through tissue (figure provided courtesy of Ohmeda, 1986).*

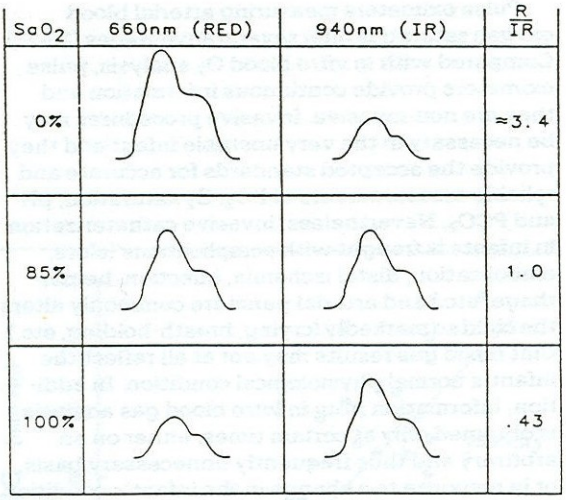


Fig. 10. *Relative pulse signal amplitudes at equal transmittance intensities for red (R) and infrared (IR) light at three different percent oxygen saturation levels (figure provided courtesy of Ohmeda, 1986).*

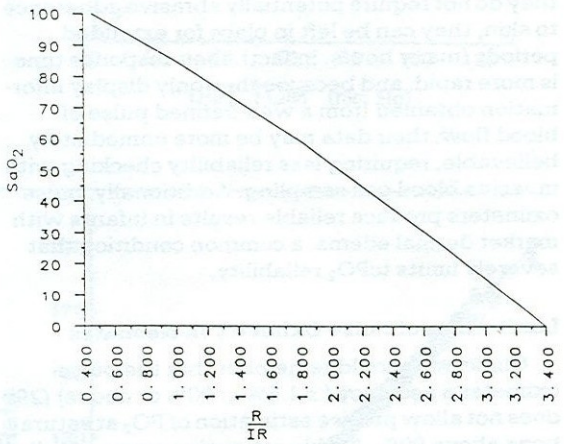


Fig.11. *Oxygen saturation of hemoglobin (SaO_2) is compared with the ratio of the plethysmographic amplitudes for red (R) and infrared (IR) light, $\frac{[R]}{[IR]}$, assuming equal intensity for each wavelength (figure provided courtesy of Ohmeda, 1986).*

Application of Pulse Oximetry

Pulse oximeters measuring arterial blood oxygen saturation offer several advantages *(20-27)*. Compared with *in vitro* blood O_2 analysis, pulse oximeters provide continuous information and they are non-invasive. Invasive procedures may be necessary in the very unstable infant and they provide the accepted standards for accurate and reliable measurements of PO_2, O_2 saturation, pH and PCO_2. Nevertheless, invasive catheterization in infants is frought with complications (clots, embolization, distal ischemia, infection, hemorrhage, etc.) and arterial puncture commonly alters the child so markedly (crying, breath-holding, etc.), that blood gas results may not at all reflect the infant's normal physiological condition. In addition, information from *in vitro* blood gas analysis is obtained only at certain times, either on an arbitrary and thus frequently unnecessary basis, or in response to a change in the infant's condition that could have been prevented (if adverse) or promoted (if beneficial) much earlier if continuous blood oxygenation information were available, as is the case with the non-invasive oximeters.

Pulse oximeters also offer favorable advantages over $tcPO_2$ instruments. The pulse oximeters do not heat or burn the very sensitive skin of babies, they do not require potentially abrasive adherence to skin, they can be left in place for extended periods (many hours, in fact), their response time is more rapid, and because they only display information obtained from a well-defined pulse of blood flow, their data may be more immediately believable, requiring less reliability checking with invasive blood gas sampling. Additionally, pulse oximeters produce reliable results in infants with market dermal edema, a common condition that severely limits $tcPO_2$ reliability.

Limitations of Pulse Oximetry in Neonates

Clinicians should remember that the pulse oximeter's accuracy ($\pm$ 1.5% at 90% or above) *(29)* does not allow precise estimation of PO_2 at saturations above 90%. At this saturation range, small O_2 saturation changes (1-2%) are associated with relatively large PO_2 changes (10-20 mmHg). This problem is particularly important in preterm infants with high HbF concentrations. Thus, pulse O_2 saturation may read less than 100% while PO_2 values are much greater than the clinically acceptable upper limits (90 mmHg). This problem is primarily of concern for the premature infant whose retinal vasculature (and perhaps other cellular membranes, e.g., those of red blood cells) can be damaged by free radicals derived from hyperoxia. Additionally, O_2 saturation may be clinically acceptable but PO_2 sufficiently low as to produce increased pulmonary vascular resistance. These two limitations to O_2 saturation oximetry suggest that in each infant, some correlation should be made between O_2 saturation and PO_2 at lower (85-88%) and higher (95-97%) saturation values before relying entirely on O_2 saturation for oxygen and/or respirator management. Such correlations are best made while the infant has an arterial catheter in place.

Other problems encountered with clinical use of pulse oximeters in neonatal patients are less significant. Jaundice artificially lowered the pulse O_2 saturation in earlier model designs but recent trials with newer models, particularly in babies, have not shown jaundice to be a major problem. On the other hand, phototherapy (bilirubin lights) can interfere with pulse O_2 saturation accuracy. This problem is easily corrected by covering the skin probe with relatively opaque material such as a diaper. Movement of the part of the body to which the probe is applied leads to a disrupted signal confined only to the time of movement. Moderate restraint can usually produce an adequate signal, or one can simply wait until movement ceases.

Finally, the geometry of the probe and the intensity of the two wavelengths of light passed through the skin limit the size of the body part for adequate application. Neonates less than 3 kg body weight, even down to 500 grams, are best studied across the palm or occasionally the anterior part of the foot. In larger infants, the palm, thumb, great toe or index finger have all been used successfully. For best application, the probe should be snug to the skin (non-adhesive elastic wrap such as Coban® by the 3-M Company works quite well) but not so tight as to cause vasoconstriction which may lead to pressure necrosis. The probe should be left in place for several seconds until movement of the extremity stops and signal stability (good visual waveform and oximeter pulse rate equal to electrical monitor heartrate) develops. One should be cautious about using increased pressure over edematous skin which may improve the pulse signal but runs a high risk of producing pressure necrosis.

Conclusion

The safety, accuracy, reliability, non-invasiveness and ease of use make pulse oximetry a valuable addition to oxygen monitoring of infants in special care nurseries. Such instruments are not as sensitive to changes in peripheral circulation or to edema, making them more reliable in sick, physiologically unstable babies and in chronically ill babies with bronchopulmonary dysplasia. Rapid and accurate measurements of O_2 saturation with such instruments in these infants can promote optimal ventilator and oxygen management. In addition, observation of changes in oxygenation during various aspects of care can help optimize care plans for each infant. Although there remains a need for knowing PO_2 in preterm infants, pulse O_2 saturation monitoring adds an important degree of control of O_2 management.

Appendix of Clinical Applications

In the following pages, figures *(12-22)* are presented which illustrate results of application of the Ohmeda Biox 3700 Pulse Oximeter with neonatal probe to premature and term infants, ranging in gestational age from 25 to 42 weeks and in weight from 500 to 5,000 grams.

Fig. 12. *This figure shows the correlation between arterial PO_2 and transcutaneous PO_2 in a large number of preterm babies of different weight, gestational age and postnatal age. Reliability of $tcPO_2$ values has been a continued problem. Calibration against arterial PO_2's obtained from invasive catheters provides the best control. Calibration of $tcPO_2$ readings against blood samples obtained by peripheral arterial puncture are frequently quite erroneous based on the considerable physiological disturbance of the infant from the manipulation and pain of the puncture. It appears far safer to use the $tcPO_2$ instruments to maintain oxygenation within a limited range, for example, between a $tcPO_2$ of 60 and 85 mmHg, as well as a trend indicator to demonstrate changes in PO_2 during adjustments in ventilator and oxygen management, changes in physiological condition, and during medical, surgical and nursing procedures.*

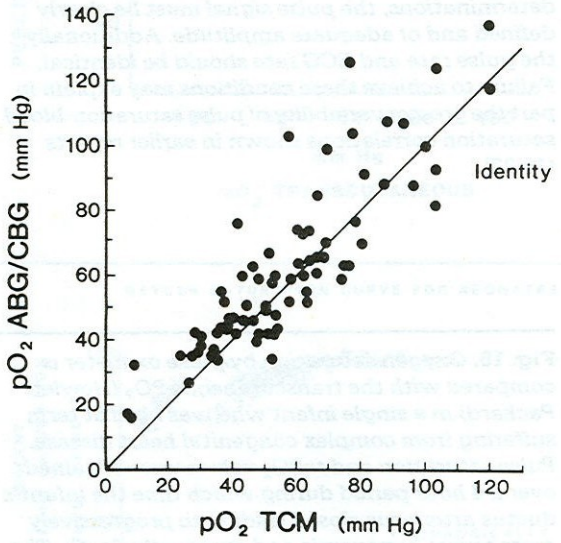


Fig. 13. *This figure shows the correlation between the heartrate obtained by the pulse oximeter and the simultaneous heartrate obtained by the electrocardiogram using a Hewlett-Packard monitor (same infants as in Fig. 12). The correlation is not different statistically from identity.*

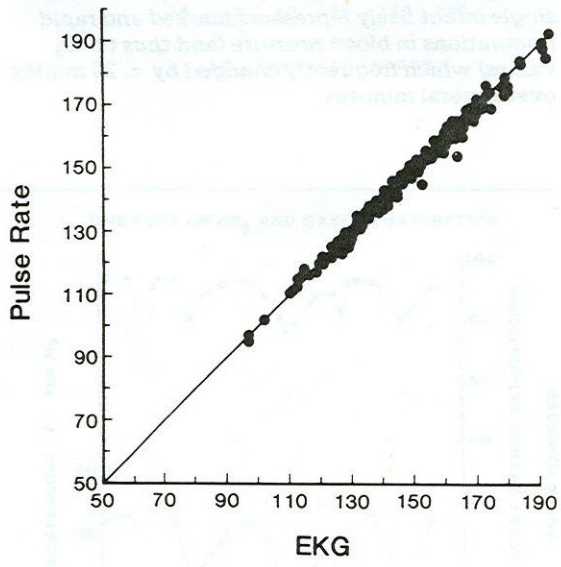


Fig. 14. *This figure presents the correlation of pulse saturation with simultaneous arterial blood gas saturation (Radiometer OSM2 Hemoximeter) obtained either from peripheral arterial puncture or from an indwelling catheter (same infants as in Fig. 12). Fifty-eight points are represented: $r = 0.948$, $p < 0.0001$, $y = 12.9 + 0.84x$. Clearly pulse oxygen saturation represents arterial saturation with good accuracy. To achieve the best correlation between pulse saturation and blood saturation determinations, the pulse signal must be clearly defined and of adequate amplitude. Additionally, the pulse rate and ECG rate should be identical. Failure to achieve these conditions may explain in part the greater variability of pulse saturation-blood saturation correlations shown in earlier reports (18,27).*

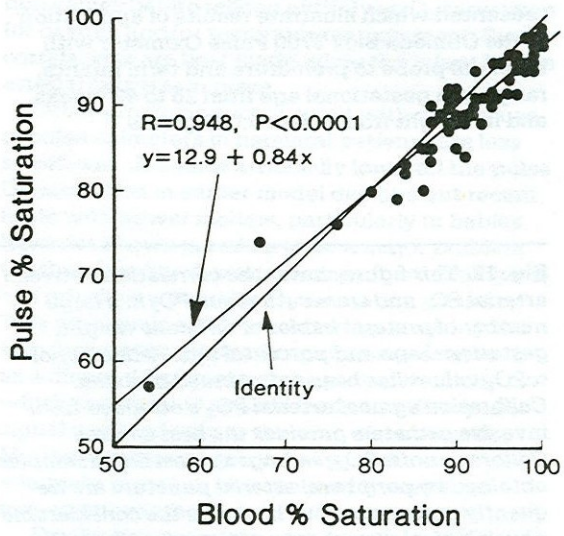


Fig. 15. *Oxygen saturation by pulse oximeter is compared with the transcutaneous PO_2 (Hewlett-Packard) in a single infant who was born at term suffering from complex congenital heart disease. Pulse saturation and $tcPO_2$ values were obtained over a 4 hour period during which time the infant's ductus arteriosus closed leading to progressively more severe hypoxemia and eventually death. The pulse saturation-$tcPO_2$ relationship shown for this infant is representative of the high affinity of fetal hemoglobin. The variability of data points for this single infant likely represents marked and rapid fluctuations in blood pressure (and thus $tcPO_2$ values) which frequently changed by* ± 20 mmHg over several minutes.

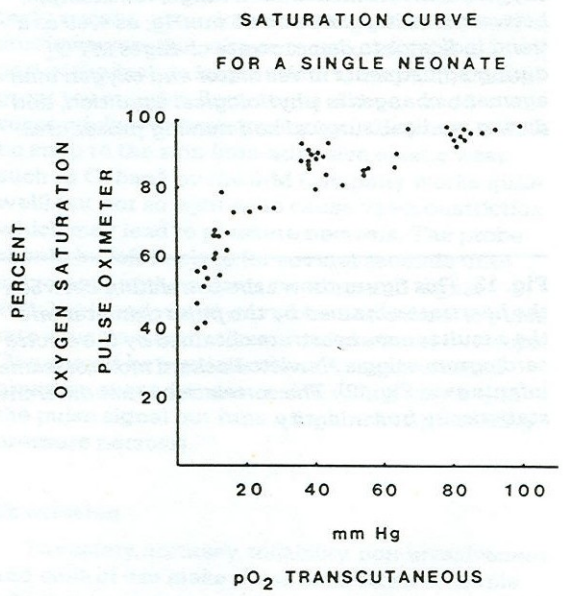


Fig. 16. *Pulse oxygen saturation and $tcPO_2$ data from the previous infant (Figure D) with high affinity blood (closed circles) are compared with pulse oxygen saturation in $tcPO_2$ values from a preterm infant who suffered from erythroblastosis fetalis and required two complete exchange transfusions during the immediate neonatal period. Following the two exchange transfusions, it is clear that the Hb-O_2 affinity is increased ("shifted to the right"), more representative of the adult hemoglobin in the blood which was used in the exchange.*

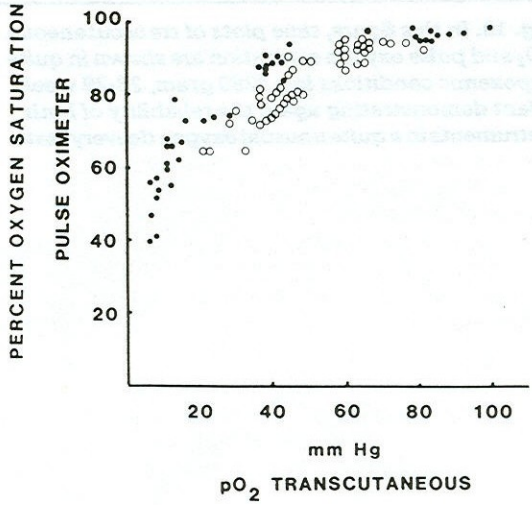


Fig. 17. *Pulse oxygen saturation and $tcPO_2$ values are shown for a large variety of preterm infants from 5 days to 30 days postnatal life (closed circles). It is clear that PO_2 values considerably greater than 100 mmHg cannot be distinguished by oxygen saturation measurements. In addition, the variability in saturation-PO_2 values between PO_2's of 20 and 60 probably reflects different mixtures of fetal and adult hemoglobin in these postnatal infants. Finally, as shown by the data presented by stars, chronically hypoxic infants may maintain their high affinity of hemoglobin for oxygen. The mechanisms for this maintenance of high affinity are not known. This particular infant suffered severe chronic, and eventually fatal, bronchopulmonary dysplasia. Data were obtained during the final two weeks of life when 100% inspired oxygen and maximal ventilator support failed to alter the infant's progressive hypoxemia.*

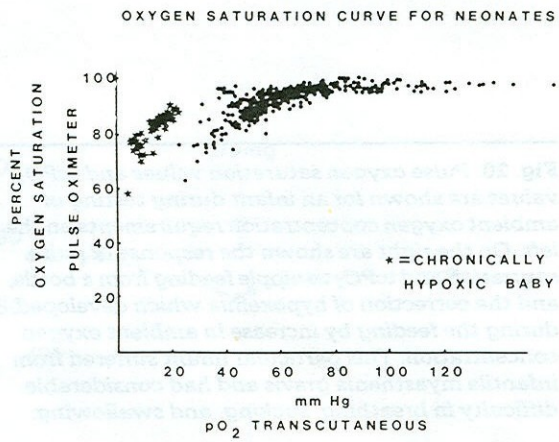


Fig. 18. *This figure shows a time plot of $tcPO_2$ (Hewlett-Packard) and pulse oxygen saturation in a 1050 gram, 27 weeks preterm infant. The two time plots are nearly mirror images of each other demonstrating the reliability of each instrument to detect quite rapidly changes in blood oxygen transport.*

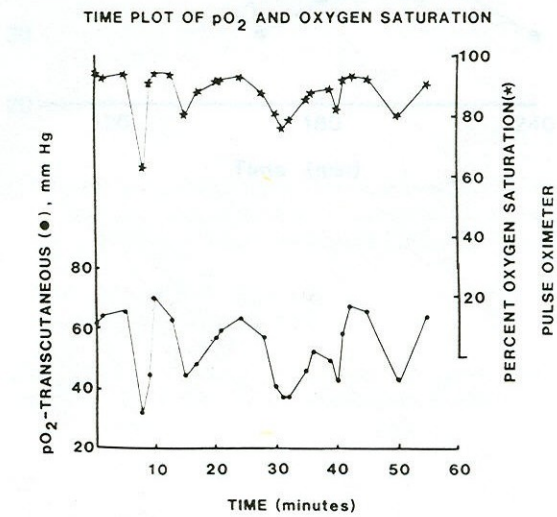


Fig. 19. *In this figure, time plots of transcutaneous PO_2 and pulse oxygen saturation are shown in quite hypoxemic conditions in a 1280 gram, 28-29 week infant demonstrating again the reliability of both instruments in a quite unusual oxygen delivery state.*

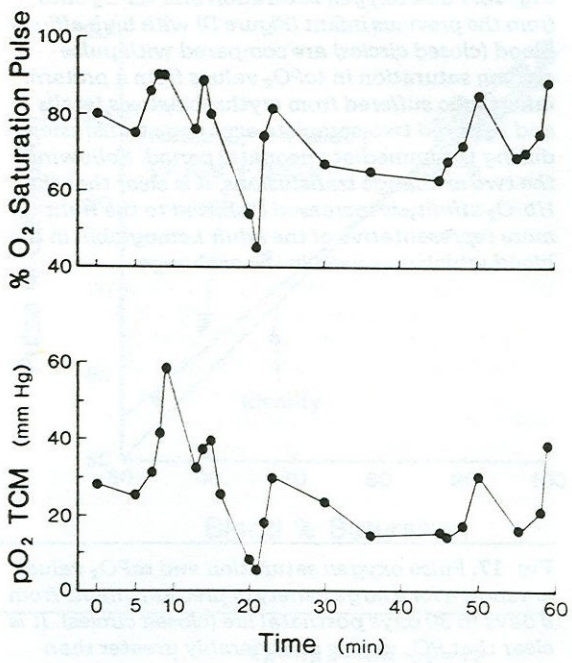


Fig. 20. *Pulse oxygen saturation values and $tcPO_2$ values are shown for an infant during testing of ambient oxygen concentration requirements on the left. On the right are shown the response of pulse saturation and $tcPO_2$ to nipple feeding from a bottle, and the correction of hypoxemia which developed during the feeding by increase in ambient oxygen concentration. This particular infant suffered from infantile myasthenia gravis and had considerable difficulty in breathing, sucking, and swallowing.*

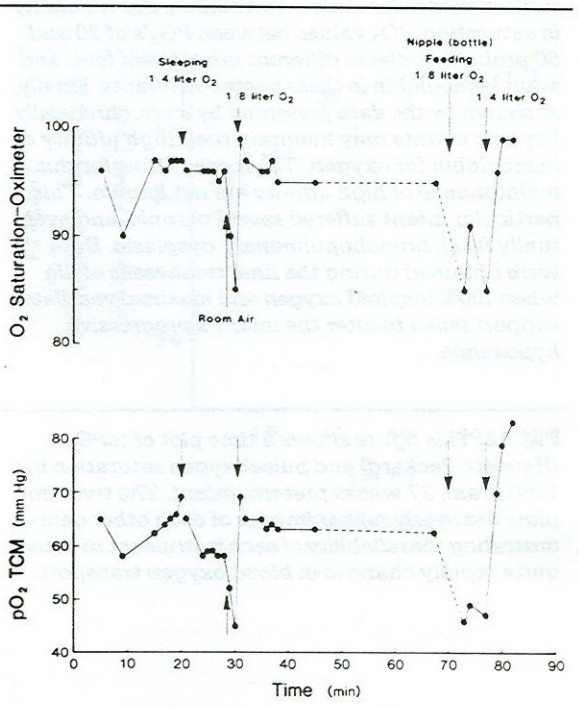
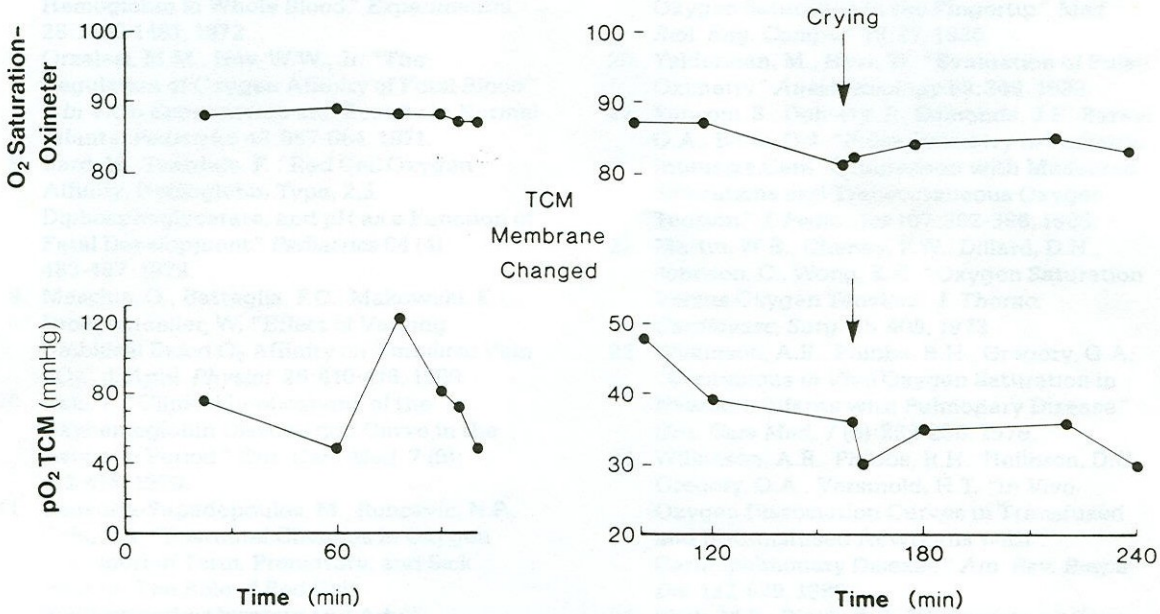


Fig. 21. *In this figure, pulse oxygen saturation values in the left panel appear normal over a 1 hour period. Simultaneous $tcPO_2$ values did not correlate well and demonstrated excessive variability. It was found on close inspection that there was an air leak under the adhesive of the $tcPO_2$ probe. With correct placement of the $tcPO_2$ probe (shown in the right panel) greater trend reliability is demonstrated for the $tcPO_2$, particularly in relationship to the pulse oximeter. This infant suffered from marked hypoxemia due to severe hyaline membrane disease. Crying quite clearly produced hypoxemia. The present study indicated that the baby was receiving inadequate oxygenation.*



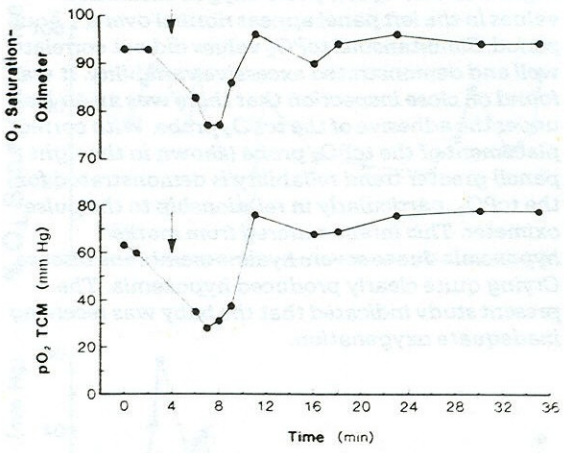


Fig. 22. *In this figure, marked hypoxemia is shown by both pulse saturation and $tcPO_2$ in response to endotracheal tube suctioning (at arrow). The hypoxemia was brief and oxygen values returned to normal within 2 minutes after suctioning was stopped. Nevertheless, these data show how rapidly and how markedly hypoxemia may develop in oxygen and ventilator-dependent infants in response to rather brief and routine respiratory care procedures. Such change in oxygenation can be detected quickly and accurately and proper oxygenation achieved and maintained by oximetry.*

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