New Developments in Oxygen Transport and Monitoring

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In this lecture we will review recent advances in the monitoring of patient oxygenation. The transport of oxygen from the atmosphere to the mitochondrion will be discussed, and monitors that function at each of four stages of the transport process will be described. These four stages include respired gas, arterial blood, tissue, and venous blood. Respired gas monitors will be mentioned only briefly. Recent developments in pulse oximetry will be reviewed in detail. Continuous intraarterial blood gas sensors will be contrasted with other arterial oxygen monitors. We will also cover tissue oxygen monitoring and mixed-venous oximetry.

Oxygen In Arterial Blood: 1. Pulse Oximetry

Physiology

The standard equation for arterial blood oxygen content shows that approximately 99% of the arterial oxygen is normally in the form of hemoglobin-bound oxygen:

$$Cao_2 = 1.38(Sao_2/100)(Hb) + 0.003\ Pao_2 . \quad (1)$$

Cao_2 is the arterial oxygen content in mL per 100 mL of blood (also called vols%), Sao_2 is the arterial hemoglobin saturation as a percentage, Hb is the total hemoglobin concentration in grams per 100 mL, and Pao_2 is the arterial blood oxygen tension in mm Hg.

The normal relationship between Sao_2 and Pao_2 is the familiar oxyhemoglobin dissociation curve. Three convenient reference points on this curve are Pao_2 = 27, Sao_2 = 50%; Pao_2 = 40, Sao_2 = 75%; and Pao_2 = 60, Sao_2 = 90%. At Pao_2 values greater than 90 mm Hg, Sao_2 is nearly 100% and thus becomes almost independent of Pao_2. It is important to remember this fact during Sao_2 monitoring in the operating room, where elevated FIo_2 values tend to yield Pao_2 values well above 90 mm Hg most of the time.

Knowledge of the relationship of hemoglobin saturation and Pao_2 allows us to predict the physiologic limitations of pulse oximetry. For example, the pulse oximeter will give no indication of early trends in Pao_2 during anesthesia at elevated inspired oxygen fraction (FIo_2) until Pao_2 values <90 mm Hg are reached. In an animal experiment, endobronchial intubations at FIo_2 values greater than 30% were usually undetected by the pulse oximeter (1).

Technology

Oximetry determines the blood concentrations of various hemoglobin species by measuring the absorbance of light at multiple wavelengths. The number of wavelengths used must be equal to or greater than the number of hemoglobin species present. A laboratory CO-oximeter, which uses four or more wavelengths, can measure the concentrations of reduced hemoglobin, O_2Hb, MetHb, and COHb. If all four of these hemoglobins are present in significant concentrations, then an oximeter must utilize at least four wavelengths to determine the concentration of any of the four species.

The pulse oximeter is a two-wavelength oximeter that functions *in vivo*. Conventional pulse oximetry determines the fluctuating or "AC" component of the light absorbance signal. At each of its two wavelengths the oximeter divides this AC signal by the corresponding "DC" component to obtain a "pulse-added absorbance." It then calculates the ratio of the pulse-added absorbances for the two wavelengths, and this ratio R is related to Sao_2 by a built-in calibration algorithm. The resulting pulse oximeter saturation is called Spo_2. The calibration curve of the pulse oximeter is empirical, based on human volunteer experimental data.

Sources of Error

Dyshemoglobins. As noted above, the pulse oximeter employs two wavelengths and can thus distinguish only two hemoglobin species: Hb and O_2Hb. If either COHb or MetHb is present, the pulse oximeter effectively has fewer equations than unknowns, and it is unable to find any of the hemoglobin concentrations. It is not clear *a priori* how the pulse oximeter will behave in the presence of various dyshemoglobins.

Two animal experiments have characterized pulse oximeter behavior during dyshemoglobinemias. In one study, dogs were exposed to carbon monoxide over 4 h (2). At lethal carboxyhemoglobin levels of 70%, the Spo_2 values were roughly 90% while the actual Sao_2 was 30%. The pulse oximeter thus "sees" COHb as if it were composed mostly of O_2Hb. In a similar experiment, high MetHb levels were achieved in dogs using benzocaine (3). As hypoxia was worsened by lowering Fio_2, Spo_2 failed to measure either functional or fractional saturation. Clinical case reports have supported the results of these studies.

IV Dyes. As abnormal hemoglobin species can affect the accuracy of pulse oximetry, so can IV dyes injected during surgery or critical care. Two studies found that IV methylene blue causes large decreases in displayed Spo_2 without changes in actual saturation and that indocyanine green causes smaller false decreases in Spo_2 (4,5).

Reductions in Peripheral Pulsation, Ambient Light. Several studies have examined the effects of low perfusion on Spo_2 (6,7). In a clinical study in the critically ill under a wide range of hemodynamic conditions, extremes in systemic vascular resistance were associated with loss of pulse oximeter signal or decreased accuracy. During reduced pulse amplitude, pulse oximeters may become sensitive to external light sources, such as fluorescent room lights (8). Most pulse oximeters actually measure and correct for ambient light intensity many times per second.

Motion Artifact. Patient motion, which causes a large fluctuating absorbance signal, is a challenging artifact. Motion artifact rarely causes difficulty in the operating room, but in the recovery room and intensive care unit it can make the pulse oximeter useless. Design engineers have tried several approaches to this problem, beginning with increasing the signal averaging time. Most pulse oximeters now allow the user to select one of several time-averaging modes. Masimo, Inc. has developed a new approach to the analysis of the oximeter light absorbance signals using adaptive digital filtering. This has led to improved performance during motion artifact, both in laboratory studies (9) and in the neonatal intensive care unit (10). This new technology has spurred other manufacturers (e.g., Nellcor, Philips, Datex-Ohmeda, Novametrix) to redesign their own signal analysis methods so that the new generation of pulse oximeters will have improved reliability and accuracy during both motion and low perfusion. These improvements in reliability and accuracy will improve the quality of care and reduce the need for frequent arterial blood-gas analysis (11).

Venous Pulsations. Conventional pulse oximeter design is based on the assumption that the pulsatile component of the light absorbance is attributable entirely to arterial blood. However, the light absorbance of venous blood can also pulsate, and this may affect Spo_2 values under some conditions (12). The Spo_2 may read falsely low values in circumstances leading to venous congestion, particularly in sensors located on the head or face. The Masimo algorithm assumes that both venous and arterial absorbances are pulsatile, and it measures their contributions independently.

Penumbra Effect. When a pulse oximeter sensor is not properly positioned on the finger or earlobe, light traveling from the source to the detector may pass through tissue at a grazing incidence. This "penumbra effect" reduces the signal-to-noise ratio and may result in Spo_2 values in the low 90s in a normoxemic subject. More concerning, a volunteer study has shown that in hypoxemic subjects, this effect can cause Spo_2 to either overestimate or underestimate actual Sao_2 values, depending on the specific instrument (13). Thus, a pulse oximeter with a malpositioned sensor may tell the clinician that a patient is only mildly hypoxemic when in fact he or she is profoundly so.

Oxygen In Arterial Blood: 2. Continuous Intraarterial Po_2

There have been numerous attempts to monitor intraarterial Po_2 using miniaturized probes passed through arterial cannulas. The first practical approach to this problem employed Clark electrodes, the same oxygen electrode used in the conventional laboratory blood-gas analyzer. Although miniaturized Clark electrodes have been used in clinical studies, the technique has never achieved popularity owing to problems with calibration drift and thrombogenicity (14). More recently, the principle of fluorescence quenching has been used to develop fiberoptic "optodes" that can continuously monitor pH, $Paco_2$, and Pao_2 through a 20-gauge arterial cannula.

Technical Considerations

Fluorescence quenching is a result of the ability of oxygen or other molecules to absorb energy from the excited states of a fluorescent dye, thus preventing this energy from being radiated as light. Lubbers developed the first fluorescence quenching "optode" that simultaneously measured Po_2 and Pco_2 in gases or liquids (15). In the 1980s optodes were successfully miniaturized, and a number of intraarterial studies were reported in both animals and humans (16,17).

Clinical Studies

Several clinical studies have demonstrated the utility of intraarterial optodes in the operating room (18). The error of optode Po_2 values is lowest at low oxygen tensions. This is a useful characteristic of these sensors. The accuracy of the optode can be within the

clinically acceptable range, especially when 18-gauge radial artery cannulas are used. Accuracy seems to be lower when 20-gauge cannulas are used. The optode can display blood-gas data continuously at the bedside, with a time response measured in seconds. However, the high costs of the disposable sensors (approximately $300 each) and their inconsistent reliability have caused intraarterial optodes to nearly disappear from the market. Optodes have other promising applications in tissues and organs that may be realized in the future. They are being marketed today for measuring the viability of tissue grafts and surgical flaps.

Oxygen In Tissue: Transcutaneous Oxygen

Physiology

The transcutaneous oxygen sensor is a Clark electrode that measures oxygen diffusing to the surface of the skin from dermal capillaries. This electrode (the same as that in the blood gas analyzer) measures oxygen tension, which is an important distinction from the pulse oximeter, which estimates hemoglobin saturation. The sensor must be heated to at least 43°C–45°C to facilitate oxygen diffusion through the stratum corneum. Surface heating also produces a local hyperemia of the dermal capillary bed, which tends to "arterialize" the blood and cause a rightward shift in the oxyhemoglobin dissociation curve. These effects, which tend to increase transcutaneous oxygen tension ($Ptco_2$), are counterbalanced by effects that decrease it, namely diffusion gradients and metabolic oxygen consumption by the skin. In neonates the competing effects nearly balance, and $Ptco_2$ is roughly equal to Pao_2. In adults, the stratum corneum is thicker and $Ptco_2$ is therefore lower than Pao_2. The transcutaneous index, $Ptco_2/Pao_2$, has average values of 1.0 in neonates, 0.9 in pediatric patients, 0.8 in adults, and 0.6 to 0.7 in the elderly.

The most serious problem with the interpretation of $Ptco_2$ is its dependence upon both cardiac output and skin perfusion. Both human and animal studies have shown that the transcutaneous index falls when the cardiac index decreases below its normal range (19,20). Studies of animals during hypovolemic shock have shown that $Ptco_2$ closely follows changes in oxygen delivery, i.e., the product of cardiac output and arterial oxygen content (19). In other words, $Ptco_2$ monitors oxygen delivery to the tissues rather than oxygen content of arterial blood.

Technical Problems

There are several practical problems associated with the use of $Ptco_2$ sensors. The electrode must be calibrated before each application to the skin. After application, the sensor requires a 10–15 min warm-up period. In pediatric patients this warm-up period is closer to 5 min. The sensor's membrane and electrolyte must be replaced periodically. The heated $Ptco_2$ electrode can cause small (0.5 cm) skin burns, particularly at temperatures of 44°C or greater. Lower probe temperatures (43°C or 43.5°C) should be used on premature infants and neonates, and the probe site should be changed every 2 to 3 h. In adults with a sensor temperature of 44°C, we have used the same location for 6–8 h with no incidence of burns.

Conclusions: $Ptco_2$ and Spo_2

$Ptco_2$ provides continuous, noninvasive monitoring of oxygen delivery to tissues. By contrast, Spo_2 (pulse oximetry) monitors arterial hemoglobin saturation, which by itself does not determine O_2 delivery. The dependence of $Ptco_2$ on both skin perfusion and Pao_2 makes it more difficult to interpret changing values. If $Ptco_2$ is normal or high, we know that the tissues are well oxygenated. When $Ptco_2$ decreases, it is a sign that either Pao_2 or blood flow is decreasing—it is up to us to determine the cause.

In the near future, we expect to see new developments in organ-specific oxygen monitors, permitting us to measure the status of the brain, heart, kidneys, and other vital organs or tissues.

Oxygen In Venous Blood: Pulmonary Artery Oximetry

Physiology of Mixed Venous Saturation

Blood oxygen saturation SO_2 is related to blood oxygen content $C(O_2)$ by the equation:

$$C(o_2) = 1.38 \cdot Hb \cdot So_2/100 + 0.003 \cdot Po_2, \quad (1a)$$

where Hb is hemoglobin in gm/dL, SO_2 is %saturation, and Po_2 is oxygen tension in mm Hg. Inserting typical arterial values (Hb = 15, Sao_2 = 98%, Pao_2 = 95 mm Hg), we find Cao_2 = 20.6 cc/dL. The corresponding venous oxygen content value (with Svo_2 = 75%, Pvo_2 = 40 mm Hg) is Cvo_2 = 15.6 cc/dL.

The total oxygen transport to the tissues, or oxygen delivery, is given by:

$$Do_2(cc/min) = C.O.(L/min) \cdot CaO_2(cc/dL) \cdot 10(dL/L), \quad (2)$$

where CO is cardiac output in L/min. For example, if CO = 5 L/min and Cao_2 = 20.6 cc/dL, then Do_2 = 1030 cc/min. Finally, we can obtain the oxygen consumption ($\dot{V}o_2$) by subtracting the oxygen returned in

venous blood (Ro_2) from the arterial oxygen delivery (Do_2):

$$\begin{aligned} VO_2 &= Do_2 - RO_2 \\ &= C.O. \cdot CaO_2 \cdot 10 - C.O. \cdot CvO_2 \cdot 10 \\ &= 10 \cdot C.O. \cdot (CaO_2 - CvO_2) \\ &= 13.8 \cdot Hb \cdot C.O. \cdot (Sao_2 - Svo_2)/100 . \end{aligned} \quad (3)$$

In the last step, we have neglected the small contribution of dissolved oxygen content ($0.003 \cdot Po_2$) and replaced $C(O_2)$ with $1.38 \cdot Hb \cdot SO_2$. In a "normal" patient having the values given above, we obtain:

$$\begin{aligned} Vo_2(\text{normal}) &= 13.8 \cdot 15 \cdot 5 \cdot (.98 - .75) \\ &= 238 \text{ cc/min} . \end{aligned}$$

During exercise, healthy individuals can increase both cardiac output and the difference ($Sao_2 - Svo_2$) by a factor of three:

$$\begin{aligned} Vo_2(\text{maximum}) &= 13.8 \cdot 15 \cdot 15 \cdot (.98 - .31) \\ &= 2{,}080 \text{ cc/min} . \end{aligned}$$

That is, $\dot{V}o_2$ can increase at least ninefold. Note that Svo_2 has fallen to 31% in this highly stressed subject, representing maximum theoretical oxygen uptake by tissue.

When oxygen consumption falls behind oxygen demand, lactic acidosis will develop, eventually leading to death if the problem is not corrected. When this begins to occur in disease (e.g., anemia), the patient will attempt to compensate and maintain oxygen consumption by using the same two mechanisms shown above: increasing CO and/or decreasing Svo_2. In the case of anemia, this compensation can maintain normal oxygen consumption even at hemoglobin values below 3 gm/dL! Thus a decrease in Svo_2 indicates that a patient is using "oxygen reserves" to compensate for a supply/demand imbalance. Decreasing oxygen supply can result from low cardiac output, low Hb, abnormal Hb (e.g., carboxyhemoglobin), or low Pao_2. Increasing oxygen demand can result from fever, malignant hyperthermia, thyrotoxicosis, or shivering.

All of the above are causes of a fall in Svo_2 but what causes Svo_2 to rise above its normal range of 68%–77%? In general, high Svo_2 values result from decreased oxygen tissue uptake, peripheral arteriovenous shunting, or inappropriate increases in cardiac output. Clinical conditions that produce elevated Svo_2 thus include sepsis, Paget's disease of bone, excessive use of inotropes, cyanide poisoning, and hypothermia. A wedged pulmonary artery catheter will also cause a high Svo_2 reading, but this is a measurement artifact.

The relationship between Svo_2 the other oxygen variables is best seen by solving our oxygen consumption equation 3 for Svo_2:

$$Svo_2 = Sao_2 - Vo_2/[13.8 \cdot Hb \cdot C.O.] \quad (4)$$

Svo_2 thus depends on $\dot{V}o_2$, Hb, CO, and Sao_2—all of which can vary in an ill patient.

Technical Considerations

Pulmonary artery Svo_2 catheters use the technology of reflectance spectrophotometry; that is, they measure the color of the blood in a manner similar to pulse oximetry. Modern Svo_2 catheters use fiberoptic bundles to transmit and receive light from the catheter tip. Light-emitting diodes provide monochromatic light sources at two or three known wavelengths. A theoretical advantage of the three-wavelength system is that its measurements should not depend upon the hemoglobin value (21). One technical problem in Svo_2 catheters is the so-called "wall artifact," whereby reflection from a vessel wall can produce a signal that is interpreted as an Svo_2 of 85%–90%. This problem has been reduced by the addition of digital filtering to the processor, which edits out sudden stepwise increases in Svo_2. However, a persistently high Svo_2 value should alert the user that the pulmonary artery catheter may be in the wedged condition, hence producing wall artifact.

Applications and Limitations

Let us consider some clinical examples of continuous Svo_2 monitoring in the operating room and intensive care unit, bearing in mind equation 4. Whenever Svo_2 changes, we should ask ourselves which terms in equation 4 are responsible. In the operating room, the terms most likely to change significantly are CO and Hb. During general anesthesia, Sao_2 and $\dot{V}o_2$ are usually constant, with the exception that $\dot{V}o_2$ will fall during hypothermia. In the intensive care unit, however, any of the four variables (CO, Hb, $\dot{V}o_2$, Sao_2) can change. Patients in respiratory failure will have varying degrees of arterial desaturation. Note that Svo_2 is directly coupled to Sao_2; that is, if Sao_2 falls by 20% and nothing else changes, Svo_2 will fall by 20%. Intensive care unit patients also have frequent changes in $\dot{V}o_2$, which may be increased by agitation, shivering, coughing, fever, pain, seizures, defecation, or lunch, to name just a few possibilities.

Continuous Svo_2 is a valuable adjunct in the management of ventilator-dependent patients. As we slowly increase positive end-expiratory pressure to improve oxygenation in the ARDS patient, Sao_2 will generally increase, but eventually CO will decrease

as venous return is compromised. At this point, oxygen delivery to tissue may begin decreasing even though Sao_2 is still increasing. Svo_2 is a reflection of oxygen delivery in this case and can thus provide a means of "optimizing" positive end-expiratory pressure without serial blood gases and cardiac output measurements.

An important limitation of pulmonary oximetry is measurement error resulting from unknown light absorbers (or reflectors) in the blood. Just as pulse oximeters are confused by the presence of IV dyes or dyshemoglobins, we have shown in animals that even a three-wavelength Svo_2 system yields large errors in the presence of significant levels of methemoglobin (3).

In summary, continuous Svo_2 is another valuable oxygen transport monitor for the operating room and the intensive care unit. To benefit most from this device, we must thoroughly understand the physiology of Svo_2 and how it relates to other cardiopulmonary variables.

The monitoring of patient oxygenation has progressed in the past 20 yr from simple measurement of FIo_2 to routine monitoring of oxygen in both arterial and venous blood. Ideally, the next 20 yr will witness the development of monitors that determine the oxygen status of each of the vital organs, allowing us to treat oxygen delivery problems when and where they occur.

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