Recent Developments in Oxygen Monitoring

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In this lecture we shall review recent advances in the monitoring of patient oxygenation. We summarize the transport of oxygen from the atmosphere to the cell, and then describe monitors that function at four stages of the O_2 transport process.

Oxygen Transport in the Human Body

At rest we consume approximately 10^{23} molecules of oxygen per second. Our cardiopulmonary system rapidly transports this large amount of oxygen from the atmosphere to every cell in the body. Oxygen is first moved from the air to the arterial blood. The equation for arterial blood oxygen content (CaO_2) shows that approximately 99% of the arterial oxygen is bound to hemoglobin:

$$CaO_2 = 1.38(Hb)(SaO_2/100) + 0.003\ PaO_2 \quad (1)$$

where CaO_2 is oxygen content in milliliters per deciliter of blood (also called vols%); SaO_2 is arterial hemoglobin saturation in percent; Hb is the total hemoglobin concentration in grams per deciliter; and PaO_2 is arterial oxygen tension in millimeters of mercury. Inserting typical arterial values (SaO_2 = 100, Hb = 15, PaO_2 = 100), we find that normal a CaO_2 is approximately 21 ml/dl. The amount of oxygen delivered to the tissues by the arterial blood is then given by the cardiac output (CO) times the CaO_2 (neglecting the small dissolved oxygen term):

$$DO_2 = 13.8\ (CO)(Hb)(SaO_2/100). \quad (2)$$

(The factor 1.38 becomes 13.8 because Hb is measured in grams per deciliter, while CO is measured in liters per minute. There are 10 deciliters in one liter.)

Finally, the oxygen consumption by the tissues (VO_2) is determined by the difference between arterial oxygen delivery and venous oxygen return:

$$VO_2 = 13.8(Hb)(CO)(SaO_2 - SvO_2)/100. \quad (3)$$

This familiar "Fick Equation" can be solved for any of the four oxygen variables involved.

If we substitute normal resting values into equation 3, we predict a resting VO_2 of

$$VO_2 = 13.8(15\ g/dl)(5\ l/min)(99\% - 75\%)/100 = 248\ ml/min.$$

During exercise or stress we can rapidly increase our cardiac output to at least 20 l/min, and decrease venous saturation to about 40%, yielding a maximum VO_2 of:

$$VO_2 = 13.8(15\ g/dl)(20\ l/min)(99\% - 40\%)/100 = 2443\ ml/min.$$

That is, we can increase oxidative metabolism by a factor of ten – we call this "10 METS." Our ability to adjust cardiac output (CO) and mixed-venous oxygen saturation (SvO_2) can also be used to compensate for disease processes that affect other oxygen variables, such as anemia or hypoxemia. For example, consider a severely anemic patient with Hb value of 2.5 g/dl, who compensates by increasing cardiac output to 15 l/min and decreasing venous saturation to 50%:

$$VO_2 = 13.8(2.5\ g/dl)(15\ l/min)(99 - 50)/100 = 254\ ml/min.$$

This extremely anemic patient can thus maintain a normal oxygen consumption by adaptations in CO and SvO_2 that are milder than those we use during normal exercise.

Oxygen in the Arterial Blood: Pulse Oximetry

Physiologic Considerations

The normal relationship between SaO_2 and PaO_2 is the familiar oxyhemoglobin dissociation curve. Three convenient points on this curve to remember are: PaO_2 = 27 mmHg, SaO_2 = 50%; PaO_2 = 45 mmHg, SaO_2 = 75%; and PaO_2 = 60 mmHg, SaO_2 = 90%. The normal curve will be shifted towards the right by acidosis, hypercarbia, or increasing 2,3-DPG. At PaO_2 values greater than 80 mmHg, SaO_2 is nearly 100% and thus becomes virtually

independent of PaO_2. It is important to remember this fact during SaO_2 monitoring in the operating room, where typical elevated inspired oxygen fraction (F_IO_2) values will yield PaO_2 values much greater than 80 mmHg most of the time.

Knowledge of the relationship between SaO_2 and PaO_2 allows us to predict the physiologic limitations of saturation monitoring by pulse oximetry. Specifically, the pulse oximeter will provide no indication of downward trends in PaO_2 during anesthesia at elevated F_IO_2 until PaO_2 values less than 80-90 mmHg are reached. In an animal study, intentional endobronchial intubations at F_IO_2 values greater than 30% were usually not detected by the pulse oximeter.[1] This results from the fact that the PaO_2 after endobronchial intubation did not decrease below about 80 mmHg when F_IO_2 was elevated.

Technology

Oximetry, a subset of spectrophotometry, determines the concentrations of various hemoglobin species by measuring the absorbances of light at multiple wavelengths. The number of oximeter light wavelengths used must be equal to or greater than the number of hemoglobin species present in the sample. A laboratory CO-oximeter, which uses multiple wavelengths, can measure the concentrations of reduced hemoglobin, oxyhemoglobin, methemoglobin, and carboxyhemoglobin. If all four hemoglobin species are present in significant concentrations, then an oximeter must have at least four light wavelengths to determine the concentration of any of the four species.

The conventional pulse oximeter is a two-wavelength oximeter that functions *in vivo*. Conventional pulse oximetry first determines the fluctuating or "AC" component of the light absorbance signal. At each of its two wavelengths the oximeter divides the AC signal by the corresponding fixed or "DC" absorbance component, to obtain a "pulse-added absorbance." It then calculates the ratio of the two pulse-added absorbances (one for each wavelength), and this ratio R is related to arterial hemoglobin saturation by a built-in calibration algorithm. The resulting pulse oximeter saturation estimate is called SpO_2. The calibration curve of the pulse oximeter is empirical; that is, it is based on human volunteer experimental data.

Sources of Error

Dyshemoglobins: As previously noted, the conventional pulse oximeter uses two wavelengths and can distinguish only two hemoglobin species: reduced hemoglobin and oxyhemoglobin. If either carboxyhemoglobin (COHb) or methemoglobin (MetHb) is present, the pulse oximeter effectively has fewer equations than unknowns, and it cannot determine any of the hemoglobin concentrations. It is thus unclear *a priori* how the pulse oximeter will behave in the presence of these dyshemoglobins.

Two animal experiments have characterized pulse oximeter behavior during methemoglobinemia and carboxyhemoglobinemia. In one of these, dogs were exposed to carbon monoxide (220 ppm) over a 3-4 hour period.[2] At a COHb level of 70% (meaning that 70% of the animal's hemoglobin was in the COHb form), the SpO_2 values were approximately 90%, whereas the actual SaO_2 was 30%. The pulse oximeter thus "sees" carboxyhemoglobin as if it were composed mostly of oxyhemoglobin. Various clinical case reports have confirmed this finding.

In a similar animal experiment, increasing methemoglobin concentrations (up to 60%) produced SpO_2 readings that gradually decreased to about 85%.[3] As these animals were further desaturated by lowering F_IO_2 during methemoglobinemia, the pulse oximeter SpO_2 reading failed to track either functional or fractional saturation. On the other hand, the presence of fetal hemoglobin has little effect on pulse oximeter accuracy, which is fortunate in the treatment of premature neonates. There are conflicting anecdotal reports on the influence of sickle hemoglobin, and it is impossible to perform volunteer hypoxia studies on patients with sickle-cell disease.

Until recently, no commercially available pulse oximeter could measure either dyshemoglobin levels or SpO_2 in the presence of substantial levels of COHb or MetHb. Masimo Inc. (Irvine, CA) has now developed the new "Rad-57 Pulse CO-oximeter," which uses eight wavelengths of light to measure COHb, MetHb and SpO_2 simultaneously. The present author has recently studied the accuracy of Rad-57 in human volunteers, and found that it can measure both MetHb and COHb with an uncertainty equal to or less than that of conventional pulse oximeters for SpO_2.[4]

Intravenous dyes: As abnormal hemoglobin species can adversely affect the accuracy of pulse oximetry, so can intravenous dyes injected during surgery or critical care. Two studies found that intravenous methylene blue causes large, rapid decreases in displayed SpO_2 without changes in actual saturation, and that indocyanine green causes smaller false decreases in SpO_2.[5,6] Intravenous fluorescein or indigo carmine appear to have little effect.

Reductions in Peripheral Pulsation; Ambient Light: Several studies have examined the effects of low perfusion upon SpO_2.[7,8] In a clinical study of critically ill patients during 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 more sensitive to external light sources, such as fluorescent room lights.[9] Most modern pulse oximeters effectively measure and correct for ambient light intensity.

Motion artifact: Patient motion, which causes a large fluctuating absorbance signal, is a very challenging artifact for pulse oximetry. Motion artifact rarely causes great difficulty in the operating room, but in the recovery room and intensive care unit it can make the pulse oximeter virtually useless. Design engineers have tried several approaches to this problem, beginning with increasing the signal averaging time. Most current pulse oximeters allow the user to select one of several time averaging modes. However, improving motion performance by simply increasing averaging time is potentially dangerous – it can cause the instrument to miss significant but short-lived hypoxemic events, which are very common in neonates. Masimo, Inc. has developed a different approach to the analysis of the oximeter light absorbance signals, using adaptive digital filtering. This has led to improved accuracy and reliability during motion artifact, both in laboratory studies[10,11] and in the neonatal intensive care unit.[12] The new technology has spurred other manufacturers (e.g., Nellcor, Philips, Datex-Ohmeda) to improve their signal analysis methods, so that today's generation of pulse oximeters has much improved performance during motion.

Venous pulsations: Conventional pulse oximeter design assumes that the pulsatile component of tissue light absorbance is entirely caused by arterial blood. However, the light absorbance of venous blood can also have a pulsatile component, and this may affect SpO_2 values under some conditions.[13] Conventional pulse oximeters may read falsely low values or may fail to give any reading in circumstances leading to venous congestion. This can occur, for example, when using an earlobe sensor on a patient who is undergoing mechanical ventilation, or who is in the Trendelenberg position.

Penumbra effect: When a pulse oximeter sensor is not properly positioned on the finger or earlobe, the light traveling from the source to the detector may pass through the tissues at only grazing incidence. This "penumbra effect" reduces the signal-to-noise ratio, and may result in SpO_2 values in the low 90's in a normoxemic subject. More importantly, a volunteer study has shown that in hypoxemic subjects, the penumbra effect can cause SpO_2 to either overestimate or underestimate actual SaO_2 values, depending on the instrument used.[14] A pulse oximeter with a malpositioned sensor may therefore indicate that a patient is only mildly hypoxemic when in fact he or she is profoundly so.

Oxygen in the Arterial Blood: Continuous Intraarterial PO_2 Measurement.

There have been a number of efforts to monitor intraarterial oxygen tension directly and continuously, using miniaturized sensors passed through arterial cannulas. The first practical approach to this problem employed the Clark electrode, the same oxygen electrode used in the conventional laboratory blood-gas analyzer. Although miniaturized Clark electrodes have been used in several clinical studies, the technique never achieved popularity because of problems with calibration drift and thrombogenicity.[15] More recently, the principle of fluorescence quenching was used to develop fiberoptic "optodes" that can continuously monitor pH, $PaCO_2$ and PaO_2 through a 20 gauge radial artery cannula.

Fluorescence quenching is a result of the ability of oxygen (or other substances to be measured) to absorb energy from the excited states of a fluorescent dye, thus preventing this energy from being radiated as light. Lubbers and Opitz[16] developed the first fluorescence quenching optode that simultaneously measured oxygen and carbon dioxide tensions in gases or liquids. In the 1980's, optodes were successfully miniaturized for intraarterial use, and studies were reported in both animals and humans.[17,18]

Clinical Studies

Several clinical studies suggested the usefulness of intraarterial optodes in the operating room.[19] The uncertainty (random error) of optode oxygen tension values is lowest at low oxygen tensions, a characteristic of these sensors. The accuracy of the optode appeared to be within the clinically acceptable range when 18-gauge arterial cannulas were used. The optode can display complete blood-gas data continuously at the patient's bedside, with a time response measured in seconds. Nevertheless, the high costs of the disposable sensors (approximately $300 each) and their inconsistent reliability have caused the intraarterial optodes to disappear from the clinical market. These devices have other potential applications in tissues and organs, which may be realized in the future. Optode sensors are available today for assessment of the viability of tissue grafts or reimplantations.

Oxygen In Tissue: Transcutaneous Oxygen

Physiologic Considerations

The transcutaneous oxygen ($P_{tc}O_2$) sensor is a Clark electrode that measures oxygen diffusing through the surface of the skin from dermal capillaries. The sensor must be heated to at least 43°C to facilitate diffusion through the stratum corneum. Surface heating also produces hyperemia of the dermal capillaries, which tends to

"arterialize" the blood and cause a rightward shift in the oxyhemoglobin dissociation curve. These effects that tend to increase $P_{tc}O_2$ are counterbalanced by other effects that decrease it, namely diffusion gradients and metabolic oxygen consumption by the skin. In neonates, the competing effects nearly cancel and $P_{tc}O_2$ is approximately equal to PaO_2. In adults, the stratum corneum is thicker and hence $P_{tc}O_2$ is usually lower than PaO_2. The transcutaneous index, $P_{tc}O_2/PaO_2$, 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 challenges in the interpretation of $P_{tc}O_2$ values are their dependence upon cardiac output and skin perfusion. Clinical studies have shown that the transcutaneous index falls when the cardiac index decreases below its normal range.[20] Animal studies have shown that $P_{tc}O_2$ decreases when either PaO_2 or cardiac index decreases, and that it closely follows trends in oxygen delivery, (i.e. the product of CO and CaO_2).

Technical problems

There are several practical problems associated with the use of $P_{tc}O_2$ sensors. The transcutaneous electrode must be gas-calibrated before each application to the skin, and then the sensor requires a 10-15 minute warm-up period. In children, the warm-up period is usually shorter. The sensor membrane and electrolyte must be replaced at least once a week. The heated $P_{tc}O_2$ electrode can cause small skin burns, particularly at temperatures of 44°C or greater. Lower probe temperatures (43 or 43.5°C) should be used on premature infants and neonates, and the sensor location should be changed every 2 to 3 hours. In adults with a sensor temperature of 44°C, we have used the same location for 6 to 8 hours with no incidence of burns.

Summary

Transcutaneous oxygen sensors provide continuous, noninvasive monitoring of oxygen delivery to tissues. By contrast, pulse oximetry provides continuous monitoring of arterial hemoglobin saturation. The dependence of $P_{tc}O_2$ on blood flow as well as PaO_2 can make it difficult to interpret changing values. If $P_{tc}O_2$ is normal or high, we know that the tissues are well oxygenated. When $P_{tc}O_2$ is low, we must determine whether this is the result of low PaO_2 or a decrease in skin perfusion.

Oxygen in Venous Blood: Pulmonary Artery Oximetry

Physiology of mixed venous saturation

Venous oxygen saturation SvO_2 is related to venous oxygen content CvO_2 by substitution into equation 1:

$$CvO_2 = 1.38(Hb)(SvO_2)/100 + 0.003(PvO_2) \quad (4)$$

The normal CvO_2 value (using $SvO_2 = 75\%$, $PvO_2 = 40$ mmHg) is 15.6 ml/dl. If we solve equation 3 (the Fick equation) for the venous saturation (SvO_2), we obtain:

$$SvO_2 = SaO_2 - VO_2/[(13.8)(Hb)(CO)]. \quad (5)$$

Equation 5 shows how SvO_2 depends upon the four oxygen transport variables: SaO_2, VO_2, Hb, and CO.

When VO_2 demand falls behind oxygen supply, lactic acidosis will result, eventually leading to death if the problem is not corrected. When this begins to occur in disease (*e.g.* anemia), the patient's body will try to maintain normal VO_2 using the same two compensatory mechanisms described above during exercise: increasing CO and/or decreasing SvO_2. In the case of anemia, we saw that such compensation can maintain normal VO_2 values even at hemoglobin levels less than 3 g/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 may result from low CO (shock), low hemoglobin (anemia), abnormal hemoglobin (carboxyhemoglobinemia), or low PaO_2 (hypoxemia). On the other hand, increasing oxygen demand can result from fever, malignant hyperthermia, thyrotoxicosis, or shivering.

The aforementioned are possible clinical causes of a decrease in SvO_2. There are also conditions that can increase SvO_2 above its normal range of 68% to 77%. High SvO_2 values can result from decreased tissue uptake of oxygen, peripheral arteriovenous shunting, and inappropriate increases in cardiac output. Clinical conditions that produce elevated SvO_2 values 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. This is a useful artifact, since it warns the clinician of an inadvertently wedged catheter.

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. 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 wavelengths. A theoretical advantage of a three wavelength system is that its measurements should not depend upon the total hemoglobin level.[21] Another problem common to all SvO_2 catheters is the "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 effectively edits out sudden step increases in SvO_2. However, a persistently high value of SvO_2 should alert the user that the catheter is in the wedged condition, as noted above.

Applications and limitations

When interpreting continuous SvO_2 versus time tracings in the operating room and intensive care unit, we must always consider equation 5, the Fick Equation solved for SvO_2. When SvO_2 changes, we must ask which term(s) in equation 5 are responsible. In the operating room, the terms most likely to change significantly are cardiac output (CO) and hemoglobin (Hb). During general anesthesia with mechanical ventilation, SaO_2 and VO_2 are usually constant, with the exception that VO_2 will decrease during hypothermia. On the other hand, this is not the case in the intensive care unit. Patients in respiratory failure will have varying degrees of arterial desaturation (low SaO_2). Note that SvO_2 is directly related to SaO_2; if SaO_2 decreases by 20% and nothing else changes, then SvO_2 will decrease by 20%. Critical care unit patients may also have frequent changes in VO_2, which can be increased by agitation, shivering, coughing, fever, pain, seizures, eating, or defecation, to name just a few.

Continuous SvO_2 is a valuable adjunct in the treatment of ventilator-dependent patients. As positive end-expiratory pressure (PEEP) is slowly increased to improve oxygenation, SaO_2 will usually increase, but eventually the cardiac output will begin to decrease as venous return is compromised. At this point, oxygen delivery to tissue may begin to decrease (and SvO2 begins to decrease) even though SaO_2 is still increasing. SvO_2 is a reflection of oxygen delivery in this situation, and can thus be used to "optimize" positive end-expiratory pressure without the need of serial blood gases and CO measurements.

In summary, SvO_2 monitoring is a valuable technology for the operating room and the critical care unit. It reflects the overall "health" and functional state of the oxygen transport system. To realize the benefits of this monitor, we must understand the physiology of SvO_2 and how it relates to the other oxygen transport variables.

Conclusions

Monitoring of oxygen in the respired gases and arterial blood is the standard of care during all anesthetics today. None of us would consider administering general anesthesia without both an FiO_2 monitor and a pulse oximeter. Recent developments in pulse oximetry will make these instruments more reliable in moving or poorly perfused patients and those with dyshemoglobinemias, but they will still be subject to the fundamental limitations of saturation monitoring. Further advances in pulse oximetry might include the noninvasive measurement of total hemoglobin. In the near future, non-invasive monitors of oxygenation in specific organs and tissues (heart, brain) will become available. Finally, mixed venous oxygen saturation indicates how much is "left over" at the end of the oxygen transport process, which gives an indication of the status of the transport system and the degree to which reserves are being used.

References

1. Barker SJ, Tremper KK, Hyatt J, Heitzmann H: Comparison of three oxygen monitors in detecting endobronchial intubation. J Clin Monitoring 1988; 4:240-3.
2. Barker SJ, Tremper KK: The effect of carbon monoxide inhalation on pulse oximetry and transcutaneous PO_2. Anesthesiology 1987; 66:677-9.
3. Barker SJ, Tremper KK, Hyatt J: Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. Anesthesiology 1989; 70:112-7.
4. Barker SJ, Curry J, Redford D, Morgan S: Measurement of COHb and MetHb by pulse oximetry: a human volunteer study. Anesthesiology 2006: *in press.*
5. Sidi A, Rush WR, Paulus DA, et al: Effect of fluorescein, indocyanine green, and methylene blue on the measurement of oxygen saturation by pulse oximetry (abstract). Anesthesiology 1986; 65(3A):A132.
6. Scheller MS, Unger RJ, Kelner MJ: Effects of intravenously administered dyes on pulse oximetry readings. Anesthesiology 1986; 65:550-2.

7. Lawson D, Norley I, Korbon G, et al: Blood flow limits and pulse oximeter signal detection. Anesthesiology 1987; 67:599-603.
8. Narang VPS: Utility of the pulse oximeter during cardiopulmonary resuscitation. Anesthesiology 1986; 65:239-40.
9. Eisele JH, Downs D: Ambient light affects pulse oximeters. Anesthesiology 1987; 67:864-5.
10. Barker SJ, Shah NK: The effects of motion on the performance of pulse oximeters in volunteers. Anesthesiology 1997; 86:101-8.
11. Barker SJ: "Motion Resistant" pulse oximetry: A comparison of new and old models. Anesth Analg 2002; 95: 967072.
12. Bohnhorst B, Peter C, Poets CF: Pulse oximeters' reliability in detecting hypoxia and bradycardia: Comparison between a conventional and two new generation oximeters. Crit Care Med 2000; 28:1565-8.
13. Kim JM, Arakawa K, Benson KT, et al: Pulse oximetry and circulatory kinetics associated with pulse volume amplitude measured by photoelectric plethysmography. Anesth Analg 1986; 65:133-9.
14. Barker SJ, Hyatt J, Shah NK, et al: The effect of sensor malpositioning on pulse oximeter accuracy during hypoxemia. Anesthesiology 1993; 79:248-54.
15. Rithalia SVS, Bennett PJ, Tinker J: The performance characteristics of an intraarterial oxygen electrode. Intensive Care Med 1981; 7:305-7.
16. Lubbers DW, Opitz N: Die pCO_2/pO_2-optode: eine neue pCO_2 bzw. pO_2-Messonde zur Messung des pCO_2 oder pO_2 von Gasen and Flussigkeiten. Z Naturforsch 1975; 30:532-3.
17. Barker SJ, Tremper KK, Hyatt J, et al: Continuous fiberoptic arterial oxygen tension measurements in dogs. J Clin Monitoring 1987; 39:48-52.
18. Barker SJ, Tremper KK, Heitzmann HA, et al: A clinical study of fiberoptic arterial oxygen tension. Crit Care Med 1987; 15:403.
19. Barker SJ, Hyatt J: Continuous measurement of intraarterial pHa, $PaCO_2$, and PaO_2 in the operating room. Anesth Analg 1991; 73:43-8.
20. Tremper KK, Waxman K, Shoemaker WC: Effects of hypoxia and shock on transcutaneous PO_2 values in dogs. Crit Care Med 1979; 7:52.
21. Gettinger A, DeTraglia MC, Glass DD: *In vivo* comparison of two mixed venous saturation catheters. Anesthesiology 1987; 66:373-5.