Project 1: Pulse Monitor and Oximetry – Week 1

BE/EE189 Design and Construction of Biodevices

Spring 2017

Pre-lab Instructions

1. All prelab questions are to be completed individually, but you can discuss with your classmates.
2. Submit your responses as a PDF. While typed responses are preferred, if you need to, you may scan legible equations/block diagrams to include.
3. The main reference for pulse oximetry is at the end of this document.
4. Have fun!

Pre-lab Questions

A pulse oximeter measures the oxygen saturation of the blood and changes in blood volume in the tissue by measuring the plethysmograph signal. The device is based on two physical principles: (1) the presence of a pulsatile signal generated by arterial blood; (2) the fast that oxyhemoglobin (O_2Hb) and reduced hemoglobin (Hb) have different optical absorption spectra. Read the reference paper for more details.

1. The basic physical principle of oximeter is the Beer-Lambert Law, which describes the absorption of a uniform medium when light is transmitted through it. The law can be written as

$$I = I_0 e^{-\varepsilon(\lambda)\cdot C\cdot D}, \tag{1}$$

   where I is the transmitted light intensity, I_0 is the incident light intensity, $\varepsilon(\lambda)$ is the extinction coefficient (also known as an attenuation coefficient or absorptivity) of the substance at wavelength λ, C is the concentration of the absorber in the medium, and D is the thickness of the medium. Defining optical density (OD) as the negative common logarithm (i.e. base 10) of the ratio of transmitted light to incident light, write the equation for OD. How are optical density and the medium thickness related?

2. There are numerous absorptive (and scattering) factors that contribute the attenuation of light through tissue. These various contributions add to the exponent term of Eq. 1:

$$I = I_0 e^{-\sum_i \varepsilon_i(\lambda)\cdot C_i\cdot D} \tag{2}$$

   where i denotes the ith absorptive component in the tissue. Suppose that $\varepsilon_i(\lambda)$ is a different known function for each of these components and that there are 10 such components, how would you go about measuring C_i? Is it possible to find C_{10} by making just two measurements?

3. Suppose we know that concentration of the 10th component oscillates between 0 and its full value C_{10}, would you be able to determine C_{10} by making just two measurements at a single wavelength? How? You may assume that you know the times when the concentration of the 10th component reaches its respective minimal and maximal values. Why is this assumption necessary?

4. Suppose we know that concentrations of the 9th and the 10th components oscillate between 0 and their respective full values, C_9 and C_{10}. Their oscillations are exactly synchronized to each other. Is it possible to determine C_9 and C_{10} by making N measurements at only one wavelength (N = any integer)? If not, what about making M measurements at two wavelengths? What is the minimum M? You may assume that you know when the concentrations of the 9th and the 10th components are minimal and maximal.

5. You have pretty much understood the principle of pulse oximeter by finishing Q4. The pulse oximeter looks at how the transmission signal changes at two different wavelengths to determine the concentration of oxygenated and deoxygenated hemoglobin in arterial blood.

$$I(\lambda_1, \text{on}) = I_{\text{DC}}(\lambda_1) + I_{\text{AC}}(\lambda_1) = I_{\text{DC}}(\lambda_1) e^{-\left[\varepsilon_{\text{O}_2\text{Hb}}(\lambda_1) C_{\text{O}_2\text{Hb}} + \varepsilon_{\text{Hb}}(\lambda_1) C_{\text{Hb}}\right] D}, \tag{3}$$

$$I(\lambda_2, \text{on}) = I_{\text{DC}}(\lambda_2) + I_{\text{AC}}(\lambda_2) = I_{\text{DC}}(\lambda_2) e^{-\left[\varepsilon_{\text{O}_2\text{Hb}}(\lambda_2) C_{\text{O}_2\text{Hb}} + \varepsilon_{\text{Hb}}(\lambda_2) C_{\text{Hb}}\right] D}, \tag{4}$$

$$I(\lambda_1, \text{off}) = I_{\text{DC}}(\lambda_1), \tag{5}$$

$$I(\lambda_2, \text{off}) = I_{\text{DC}}(\lambda_2) \tag{6}$$

In these equations, the subscript DC refers to the baseline signal and the subscript AC refers to the pulsatile signal. Here, on and off refer respectively to the peaks and valleys of the pulsatile signal. According to the above equations, calculate the oxygen saturation, which is defined as

$$\text{SaO}_2 = \frac{C_{\text{O}_2\text{Hb}}}{C_{\text{O}_2\text{Hb}} + C_{\text{Hb}}}. \tag{7}$$

Express your result in terms of

$$R = \frac{\ln\left(\dfrac{I_{\text{DC}}(\lambda_1) + I_{\text{AC}}(\lambda_1)}{I_{\text{DC}}(\lambda_1)}\right)}{\ln\left(\dfrac{I_{\text{DC}}(\lambda_2) + I_{\text{AC}}(\lambda_2)}{I_{\text{DC}}(\lambda_2)}\right)}. \tag{8}$$

6. Simplify Eq. 8 in the case where $I_{\text{AC}}(\lambda) \ll I_{\text{DC}}(\lambda)$. This simplification is approximately correct for pulse oximetry scenario. Hint: use Taylor series.

7. In practice, SaO_2 is often obtained by an empirical calibration curve, e.g., Fig. 4 in the reference. Why is the calibration curve different from the equation that we derived above?

8. Find the optical absorption spectra of O_2Hb and Hb (cite your source). Include the spectra in your answer. Identify the appropriate wavelengths of light that can be used for the detection of each type of Hb.

9. Draw a block diagram of a typical pulse oximeter. Include hardware (e.g. light sources, detectors), signal acquisition and signal processing required to obtain the pulse rate and the oxygen saturation of the user. This should be a higher level diagram; you do not need to go into depth of the precise implementation details of each step.

10. Take a look the commercial pulse oximeter provided. Write a brief report of what each component is responsible for (e.g. light source, detector, display) Include annotated photos/drawings where possible. The report should outline how that particular pulse oximeter and its specific parts work. You do not have to tear apart the oximeter.

MEDICAL INTELLIGENCE ARTICLE

Julien F. Biebuyck, M.B., D.Phil., Editor

Anesthesiology
70:98–108, 1989

Pulse Oximetry

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PULSE OXIMETRY has been recommended as a standard of care for every general anesthetic.[1]† This technique, virtually unknown in anesthesia 5 yr ago, has been so readily adopted for several reasons. The device provides valuable data regarding blood oxygenation and this information is obtained easily, continuously, and noninvasively. The pulse oximeter is based upon two physical principles. First, the light absorbance of oxygenated hemoglobin is different from that of reduced hemoglobin at the oximeter's two wavelengths. Second, the absorbances at both wavelengths have a pulsatile (AC) component, which is the result of the fluctuating volume of arterial blood between the source and detector. Given these two facts and no other physics or physiology, the engineering design of the pulse oximeter is clever but straightforward. The purpose of this article is to review the historical development of pulse oximetry, as well as the physics and engineering principles upon which it is based. We shall also discuss selected studies that demonstrate its accuracy, limitations, and utility in the clinical setting.

History

Severinghaus and Astrup have recently reviewed in detail the development of blood gas analysis.[2] This review includes the fascinating history of oximetry and pulse oximetry, of which the following is a brief summary.

As with any new technique, many people contributed to the development of usable *in vivo* oximeters. Two early researchers who stand out are Carl Matthes and Glen Millikan. In 1935, Matthes built the first device that continuously measured human blood oxygen saturation *in vivo* by transilluminating tissue. He used two wavelengths of light: one that was sensitive to changes in oxygenation and another that was not. The second wavelength, in the infrared range, was used to compensate for changes in tissue thickness, hemoglobin content, and light intensity. This device could follow trends in saturation but was difficult to calibrate. J. R. Squires, in Great Britain, developed a similar device that was calibrated by compressing the tissue to eliminate the blood.[3] This same calibration technique was later adopted in the first oximeters used in the operating room.

In the early 1940s, Glen Millikan coined the term "oximeter" to describe a lightweight device he developed for aviation research.[4] Later in the 1940s, oximeters similar to Millikan's were used by Earl Wood and others in the operating room, where they were noted to detect significant desaturations even during routine anesthetics.[5,6] A paper published as early as 1951 in ANESTHESIOLOGY concluded prophetically that "on many occasions this instrument has detected anoxemia when observations of pulse, blood pressure, and color of the patient, and peripheral vascular tone have shown no abnormalities" (fig. 1).[6] These findings were consistent with the classic work of Comroe documenting the unreliability of cyanosis for the detection of anoxemia.[7] It was evident to these early workers that this monitor had potential clinical utility.

In its initial clinical development, the ear oximeter had several limitations. It was a delicate instrument that required a technician to operate and maintain. The earpiece was large, difficult to position, and produced enough heat to cause second degree burns on the pinna. Furthermore, it required calibration on each patient prior to use. During the 1950s, Earl Wood devised a modification of the Millikan ear piece that was used in many clinical and laboratory investigations. Although the ear oximeter showed promise in some settings, it was still considered a research tool.

In the 1970s, Hewlett-Packard® marketed the first self-calibrating ear oximeter. This device used eight wavelengths of light to determine hemoglobin saturation.[8,9] This method over-specified the system, because only four wavelengths are theoretically required to solve for hemoglobin saturation, as we shall see below. Hewlett-Packard®'s oximeter also used the method of heating the ear to "arterialize" the capillary blood. This oximeter quickly

This article is accompanied by an editorial. Please see: Fairley HB: Changing perspectives in monitoring oxygenation. ANESTHESIOLOGY 70:2–4, 1989.

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Key words: Hemoglobin saturation. Oxygen monitoring. Pulse oximeter.

† American Society of Anesthesiologists: Standards for basic intraoperative monitoring. Anesthesia Patient Safety Foundation March: 3, 1987.

became a standard clinical and laboratory tool in pulmonary medicine. Although it was demonstrated to be accurate for intraoperative monitoring,[10] its size and expense, and the cumbersome nature of the ear probe prevented its acceptance as a routine monitor. At this time, all oximeters produced various light source wavelengths by filtering white light. The filtered light was then transmitted to and from the tissue through fiberoptic cables.

In the mid 1970s, Takuo Aoyagi, an engineer working for Nihon Kohden Corporation, made an ingenious discovery regarding oximetry. He was developing a method to estimate cardiac output semi-noninvasively by detecting the washout curve of dye injected into a peripheral vein as it perfused the ear. This washout curve was measured in the ear with a red and infrared light densitometer similar to the Millikan ear oximeter. He noticed that his washout curves contained pulsations due to the arterial pulse in the ear. To more easily analyze the dye washout curve, he subtracted these pulsations from the curve, and in doing so he discovered that the absorbance ratio of the pulsations at the two wavelengths changed with arterial hemoglobin saturation. He soon realized that he could build an ear oximeter that measured arterial hemoglobin saturation without heating the ear by analyzing pulsatile light absorbances.[2] This first pulse oximeter, developed by Nihon Kohden, used filtered light sources similar to Millikan's ear oximeter. The device was evaluated clinically in the mid 1970s and marketed with little success.[2]

In the late 1970s, Scott Wilber in Boulder, Colorado, developed the first clinically accepted pulse oximeter by making two modifications of the Nihon Kohden method.[11]‡ First, he produced a lightweight sensor by using light emitting diodes (LEDs) as light sources and photodiodes as detectors. Consequently, the instrument was connected to its earclip sensor only by a small electrical cable. Wilber also improved the saturation estimates by using a digital microprocessor to store a complex calibration algorithm based on human volunteer data.[12]‡ This method will be discussed in more detail below. This device was developed by Biox Corporation of Boulder, Colorado, and was successfully marketed to pulmonary function laboratories in the early 1980s.

The clinical utility of the noninvasive oximeter in the operating room was rediscovered in the 1980s by William New, an anesthesiologist at Stanford University. Realizing that a continuous, noninvasive monitor of oxygenation would be useful to anesthesiologists, New developed and marketed a pulse oximeter to this group.[13] The Nellcor model N100 had by 1985 become almost synonymous with the term "pulse oximeter."

‡ Wilber S: Blood constituent measuring device and method. US Patent #4, 407, 290 April 1, 1981.

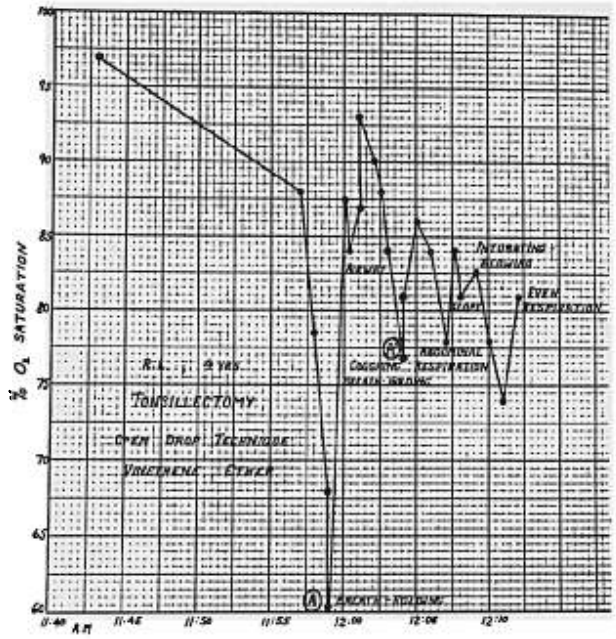

FIG. 1. This figure is from a 1951 article in ANESTHESIOLOGY. It reveals dramatic desaturation in a 4-yr-old patient during a tonsillectomy. Reproduced from Stephen RC, Slater HM, Johnson AL, Sekelj P: The oximeter—A technical aid for the anesthesiologist. ANESTHESIOLOGY 12:548, 1951, with permission.

The Physics and Physiology of Pulse Oximetry

BEER'S LAW

In the 1930s, Matthes used spectrophotometry to determine hemoglobin oxygen saturation.[2] This method is based on the Beer-Lambert law, which relates the concentration of a solute to the intensity of light transmitted through a solution.

$$I_{trans} = I_{in}e^{-A} \quad (1)$$

$$A = DC\epsilon \quad (1a)$$

where I_{trans} = intensity of transmitted light; I_{in} = intensity of incident light; A = absorption; D = distance light is transmitted through the liquid (path length); C = concentration of solute (hemoglobin); ϵ = extinction coefficient of the solute (a constant for a given solute at a specified wavelength). Thus, if a known solute is in a clear solution in a cuvette of known dimensions, the solute concentration can be calculated from measurements of the incident and transmitted light intensity at a known wavelength. The extinction coefficient ϵ is a property of light absorption for a specific substance at a specified wavelength. In a one-component system, the absorption A is the product of the path length, the concentration, and the extinction coefficient, equation 1a. If multiple solutes

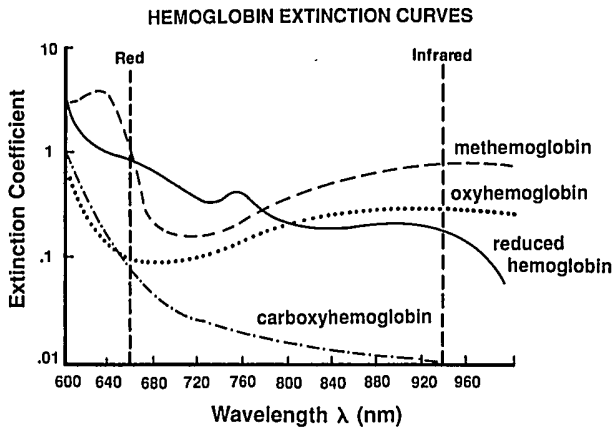

FIG. 2. Transmitted light absorbance spectra of four hemoglobin species: oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin, and methemoglobin. Adapted from Barker SJ and Tremper KK: Pulse Oximetry: Applications and limitations, Advances in Oxygen Monitoring, International Anesthesiology Clinics. Boston, Little, Brown and Company, 1987, pp. 155–175.

are present, A is the sum of similar expressions for each solute. The extinction coefficient can vary dramatically with the wavelength of the light. The extinction coefficients for various hemoglobin species in the red and infrared wavelength range are shown in figure 2.

Laboratory oximeters use this principle to determine hemoglobin concentration by measuring the intensity of light transmitted through a cuvette filled with a hemoglobin solution produced from lysed red blood cells.[14] For Beer's law to be valid, both the solvent and the cuvette must be transparent at the wavelength used, the light path length must be known exactly, and no absorbing species can be present in the solution other than the known solute. It is difficult to fulfill these requirements in clinical devices; therefore, each instrument theoretically based on Beer's law also requires empirical corrections to improve accuracy.

Hemoglobin Saturation Definitions

Adult blood usually contains four species of hemoglobin: oxyhemoglobin (O_2Hb), reduced hemoglobin (Hb), methemoglobin (MetHb), and carboxyhemoglobin (COHb) (fig. 2). The last two species are in small concentrations, except in pathologic conditions. There are several definitions of hemoglobin saturation. Historically, "oxygen saturation" was first defined as the oxygen content expressed as a percentage of the oxygen capacity. The oxygen content (cc of oxygen per 100 cc of blood) was measured volumetrically by the method of Van Slyke and Neill (1924).[15] The oxygen capacity was defined as the oxygen content after the blood sample had been equilibrated with room air (158 mmHg oxygen at sea level). By the above definition of oxygen saturation, the two forms of hemoglobin that do not bind oxygen (COHb and MetHb) are not included. This is the origin of what is now referred to as "functional hemoglobin saturation," defined as (Severinghaus JW, personal communication):

$$\text{Functional } SaO_2 = \frac{O_2Hb}{O_2Hb + Hb} \times 100\%. \quad (2)$$

With the advent of multiwavelength oximeters that can measure all four species of hemoglobin, "fractional saturation" has been defined as the ratio of oxyhemoglobin to total hemoglobin:

$$\text{Fractional } SaO_2 = \frac{O_2Hb}{O_2Hb + Hb + COHb + MetHb} \times 100\%. \quad (3)$$

The fractional hemoglobin saturation is also called the "oxyhemoglobin fraction," or "oxyhemoglobin %."[14]

When oximetry is used to measure hemoglobin saturation, Beer's law must be applied to a solution containing four unknown species: O_2Hb, Hb, COHb, and MetHb. Expanding equation 1a to a four-component system results in an absorption given by:

$$A = D_1C_1\epsilon_1 + D_2C_2\epsilon_2 + D_3C_3\epsilon_3 + D_4C_4\epsilon_4. \quad (1b)$$

The subscripts 1 through 4 correspond to the four hemoglobin species. If the path lengths are the same, then D can be factored out:

$$A = D(C_1\epsilon_1 + C_2\epsilon_2 + C_3\epsilon_3 + C_4\epsilon_4). \quad (1c)$$

The extinction coefficients ϵ_1 through ϵ_4 are constants at a given wavelength λ (fig. 2). The absorption defined in equation 1c is determined from equation 1 by measuring the incident and transmitted light intensities. From equation 1c, we see that four wavelengths of light are needed to produce four equations to solve for the unknown concentrations C_1 through C_4. If COHb and MetHb were not present, their contributions to the absorption would be zero and functional hemoglobin saturation could be determined by a two-wavelength oximeter (two equations and two unknowns). If two wavelengths existed for which the extinction coefficients for COHb and MetHb were zero, then these absorption terms would again be zero and a two-wavelength oximeter could measure functional saturation. Unfortunately, as illustrated in figure 2, the extinction coefficients for COHb and MetHb are not zero in the red and infrared range, and their presence will, therefore, contribute to the absorption. Even though the definition of functional hemoglobin saturation involves only two hemoglobin species (O_2Hb and Hb), when MetHb and COHb are present, four wavelengths are required to determine either functional or fractional hemoglobin saturation.[14]

PULSE OXIMETRY

Noninvasive oximeters measure red and infrared light transmitted through a tissue bed, effectively using the finger or ear as a cuvette containing hemoglobin. There are several technical problems in accurately estimating SaO_2 by this method. First, there are many absorbers in the light path other than arterial hemoglobin, including skin, soft tissue, and venous and capillary blood. The early oximeters subtracted the tissue absorbance by compressing the tissue during calibration to eliminate all the blood, and using the absorbance of bloodless tissue as the baseline. These oximeters also heated the tissue to obtain a signal related to arterial blood with minimum influence of venous and capillary blood.

Pulse oximeters deal with the effects of tissue and venous blood absorbances in a completely different way. Figure 3 schematically illustrates the series of absorbers in a living tissue sample. At the top of the figure is the pulsatile or AC component, which is attributed to the pulsating arterial blood. The baseline or DC component represents the absorbances of the tissue bed, including venous blood, capillary blood, and nonpulsatile arterial blood. The pulsatile expansion of the arteriolar bed produces an increase in path length (see equation 1b), thereby increasing the absorbance. All pulse oximeters assume that the only pulsatile absorbance between the light source and the photodetector is that of arterial blood. They use two wavelengths of light: 660 nanometers (red) and 940 nanometers (near infrared). The pulse oximeter first determines the AC component of absorbance at each wavelength and divides this by the corresponding DC component to obtain a "pulse-added" absorbance that is independent of the incident light intensity. It then calculates the ratio (R) of these pulse-added absorbances, which is empirically related to SaO_2:

$$R = \frac{AC_{660}/DC_{660}}{AC_{940}/DC_{940}}. \quad (4)$$

Figure 4 is an example of a pulse oximeter calibration curve.[16] The actual curves used in commercial devices are based on experimental studies in human volunteers. Note that when the ratio of red to infrared absorbance is one, the saturation is approximately 85%. This fact has clinical implications to be discussed later.

It is a fortuitous coincidence of technology and physiology that allowed the development of solid-state pulse oximeter sensors.[16] Light emitting diodes (LEDs) are available over a relatively narrow range of the electromagnetic spectrum. Among the available wavelengths are some that not only pass through skin but also are absorbed by both oxyhemoglobin and reduced hemoglobin. For best sensitivity, the difference between the ratios of the absorbances of O_2Hb and Hb at the two wavelengths should be maximized. As we see in figure 2, at 660 nanometers, reduced hemoglobin absorbs about ten times as much light as oxyhemoglobin. (Note that the extinction coefficients are plotted on a logarithmic axis.) At the infrared wavelength of 940 nanometers, the absorption coefficient of O_2Hb is greater than that of Hb.

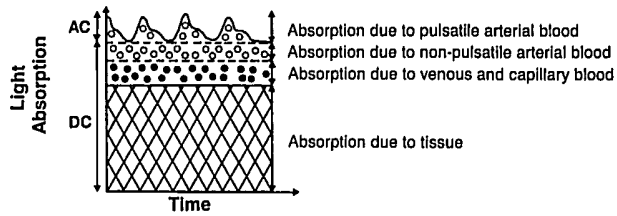

FIG. 3. This figure schematically illustrates the light absorption through living tissue. Note that the AC signal is due to the pulsatile component of the arterial blood while the DC signal is comprised of all the nonpulsatile absorbers in the tissue; nonpulsatile arterial blood, venous and capillary blood, and all other tissues. Adapted from Ohmeda Pulse Oximeter Model 3700 Service Manual, 1986, p. 22.

Engineering Design and Physiologic Limitations

Although the theory on which pulse oximetry is based is relatively straightforward, the application of this theory to the production of a clinically useful device involves a

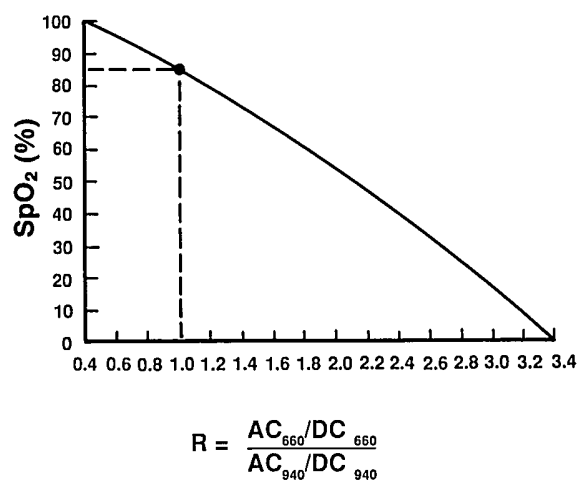

FIG. 4. This is a typical pulse oximeter calibration curve. Note that the SaO_2 estimate is determined from the ratio (R) of the pulse-added red absorbance at 660 nanometers to pulse-added infrared absorbance at 940 nanometers. The ratios of red to infrared absorbances vary from approximately .4 at 100% saturation to 3.4 at 0% saturation. Note that the ratio of red to infrared absorbance is one at a saturation of approximately 85%. This curve can be approximately determined on a theoretical basis but, for accurate predictions of SpO_2, experimental data are required. Adapted from JA Pologe: Pulse oximetry: Technical aspects of machine design, International Anesthesiology Clinics, Advances in Oxygen Monitoring. Edited by Tremper KK, Barker SJ. Boston, Little, Brown and Company, 1987, p 142.

significant engineering effort. This section will present in general terms the clinical and physiologic problems of oximeter design and their engineering solutions. The discussion is divided into four areas: dyshemoglobins and dyes, LED center wavelength variability, signal artifact management, and accuracy and response. The reader should be aware that these problems can interact with one another.

Dyshemoglobins and Dyes

Being two-wavelength devices, pulse oximeters can deal with only two hemoglobin species. As noted above, this would be adequate to measure functional SaO_2 if MetHb and COHb did not absorb red or infrared light at the wavelengths used. Unfortunately, this is not the case, and therefore both MetHb and COHb will cause errors in the pulse oximeter reading. It is not intuitively obvious how a pulse oximeter will behave in the presence of dyshemoglobins. With respect to carboxyhemoglobin, we can gain some insight from the extinction curves of figure 2. In the infrared range (940 nm), COHb absorbs very little light; whereas, in the red range (660 nm), it absorbs as much light as does O_2Hb. This is clinically illustrated by the fact that patients with carboxyhemoglobinemia appear red. Therefore, to the pulse oximeter, COHb looks like O_2Hb at 660 nm; while, at 940 nm COHb is relatively transparent. The effect of COHb on pulse oximeter values has been evaluated experimentally in dogs.[17] In this study, the pulse oximeter saturation (SpO_2) was found to be given approximately by:

$$SpO_2 = \frac{O_2Hb + 0.9 \times COHb}{\text{total Hb}} \times 100\%. \qquad (5)$$

The effects of methemoglobinemia on pulse oximetry are also partially predictable from the extinction curves (fig. 2). MetHb has nearly the same absorbance as reduced hemoglobin at 660 nm, while it has a greater absorbance than the other hemoglobins at 940 nm. This is consistent with the clinical observation that methemoglobinemia produces very dark, brownish blood. Thus, it would be expected to produce a large pulsatile absorbance signal at both wavelengths. The effect of MetHb on pulse oximeter readings has also been measured in dogs.[18] As methemoglobin levels increased, the pulse oximeter saturation (SpO_2) tended toward 85% and eventually became almost independent of the actual SaO_2.[18] In other words, in the presence of high levels of MetHb, SpO_2 is erroneously low when SaO_2 is above 85%, and erroneously high when SaO_2 is below 85%. This may be explained by the fact that MetHb causes a large pulsatile absorbance at both wavelengths, thereby adding to both the numerator and denominator of the absorbance ratio R (equation 4) and forcing this ratio toward unity. As shown in figure 4, an absorbance ratio of one corresponds to a saturation of 85% on the calibration curve. Pulse oximeter error during methemoglobinemia has also been confirmed in a clinical report.[19]

In neonatal blood, a fifth type of hemoglobin is present, fetal hemoglobin (HbF). HbF differs from adult Hb in the amino acid sequences of two of the four globin subunits. Adult Hb has two α- and two β-globin chains, while HbF has two α and two f chains. This difference in globin chains has little effect on the extinction curves and therefore should not affect pulse oximeter readings.§¶ This is indeed fortunate because the fraction of HbF present in neonatal blood is a function of gestational age and cannot be accurately predicted. HbF does produce a small error in *in vitro* laboratory oximeters; O_2HbF may be interpreted as consisting partially of COHb.[20]

The absorbance ratio R (equation 4) may be affected by any substance present in the pulsatile blood that absorbs light at 660 or 940 nm and was not present in the same concentration in the volunteers used to generate the calibration curve (fig. 4). Intravenous dyes provide a good example of this principle.[21,22] Scheller *et al.* evaluated the effects of bolus doses of methylene blue, indigo carmine, and indocyanine green on pulse oximeters in human volunteers.[21] They found that methylene blue caused a fall in SpO_2 to approximately 65% for 1–2 min. Indigo carmine produced a very small drop in saturation, while indocyanine green had an intermediate effect. The detection of intravenous dyes by pulse oximeters should not be surprising, because it was this effect that led Aoyagi to the invention of pulse oximetry.[2]

LED Center Wavelength Variability

The LEDs used in pulse oximeter sensors are not ideal monochromatic light sources; there is a narrow spectral range over which they emit light. The center wavelength of the emission spectrum varies even among diodes of the same type from the same manufacturer. This variation can be ±15 nanometers.[16] As seen in figure 2, a shift in LED center wavelength will change the measured extinction coefficient and thus produce an error in the saturation estimate. This source wavelength effect will be greatest for the red (660 nm) wavelength, because the extinction curves have a steeper slope at this wavelength. Manufacturers have found two approaches to this problem. Some test all the LEDs and reject those that are out of their specified wavelength range, *e.g.*, 660 ± 5 nanometers. This is expensive due to the number of LEDs

§ Pologe JA, Raley DM: Effects of fetal hemoglobin on pulse oximetry. J Perinat VII:324–326, 1987.

¶ Anderson JV: The accuracy of pulse oximetry in neonates: Effects of fetal hemoglobin and bilirubin. J Perinat VII:323, 1987.

rejected; *i.e.*, narrower acceptable range yields improved accuracy but also more rejected LEDs. Alternatively, other manufacturers program the pulse oximeter to accept several ranges of LED center wavelengths for both the red and infrared, allowing the device to correct internally for different wavelengths. This permits the manufacturer to use more of the available LEDs, but also requires a more sophisticated device with a mechanism for identifying the sensor LED wavelengths to the pulse oximeter.[16] Incompletely compensated LED frequency variation will not change the pulse oximeter's ability to trend saturation changes, but will produce probe to probe variability in the absolute measurement of SaO_2.[16]

Signal Artifact Management

Probably the most difficult engineering problem in pulse oximeter design is the identification of the "ripple" absorbance pattern of the arterial blood in a "sea" of electromagnetic artifact. Artifact has three major sources: ambient light, low perfusion (low AC/DC signal), and motion (large AC/DC signal).[16] All of these result in poor signal-to-noise ratio.

The photodiodes used in the sensor as light detectors cannot discriminate one wavelength of light from another. Therefore, the detector does not know whether received light originates from the red LED, the infrared LED, or the room lights. This problem is solved by alternating the red and infrared LED. The red LED is turned on first and the photodiode detector produces a current resulting from the red LED plus the room lights. Next, the red LED is turned off and the infrared LED is turned on, and the photodiode signal represents the infrared LED plus the room lights. Finally, both LEDs are turned off and the photodiode generates a signal from the room lights alone. This sequence is repeated hundreds of times per second.[16] In this way, the oximeter attempts to eliminate light interference even in a quickly changing background of room light. Some fluctuating light sources can cause problems in spite of this clever design.[23–25] Clinically, ambient light artifact can be minimized by covering the sensor with an opaque shield.[26]

Another engineering problem is that of low AC-to-DC signal ratio. When a small pulsatile absorbance signal is detected, the pulse oximeter will amplify that signal and estimate the saturation from the ratio of the amplified absorbances. The pulse oximeter can thereby estimate saturation values for a wide range of patients with differing pulsatile absorbance amplitudes. Unfortunately, as with a radio receiver, when a weak signal is amplified, the background noise (static) is also amplified. At the highest amplifications (which can be as much as a billion times), the pulse oximeter may analyze this noise signal and generate an SpO_2 value from it.[11] This problem could be demonstrated in early pulse oximeters by placing a piece of paper in the sensor between the photodiode and the LED. Most early models would amplify the background noise in searching for a pulse until they eventually displayed a pulse and saturation value. To prevent this type of artifact, manufacturers have now incorporated minimum values for signal-to-noise ratio, below which the device will display no SpO_2 value. Some oximeters also display a low signal strength error message, and some display a plethysmographic wave for visual identification of noise.

Several studies have examined the effect of low perfusion on pulse oximeter estimates.[27–31]**†† Animal experiments have demonstrated that, during hemorrhagic shock, pulse oximeters may underestimate saturation or lose signal altogether.**†† In one clinical study of pulse oximeter accuracy in the critically ill under a wide range of hemodynamic conditions, extremes in systemic vascular resistance were associated with loss of signal or decreased accuracy.[27] In these and most other studies of pulse oximeter accuracy, data were collected only when the pulse oximeter heart rate equalled the EKG heart rate. It has been assumed that this is a necessary condition for accuracy because it implies that the pulse oximeter is detecting pulses produced by heartbeats.

Since the device automatically increases its amplification as the pulse signal decreases, the pulse oximeter display should be relatively insensitive to changes in perfusion. Nevertheless, several clinical studies have used the pulse oximeter to assess the adequacy of peripheral perfusion.[29–31] One study even employed this device to evaluate perfusion in reimplanted extremities.[32] As with any plethysmograph, the pulse oximeter will detect a complete loss of peripheral pulse. However, it was not designed to monitor peripheral blood flow, as has been illustrated by Lawson *et al.*[28] They determined the peripheral blood flow lower limit at which a pulse oximeter ceased detecting pulses. The blood flow was assessed at the finger by a laser-doppler flow probe as a blood pressure cuff was inflated. The pulse oximeter stopped detecting pulses when blood flow had decreased to 8.6% of its control value, which occurred when the pressure cuff was inflated to 96% of the control systolic pressure. When the tourniquet was slowly released from full occlusion, the pulse oximeter regained a pulse and saturation value when blood flow was only 4% of the baseline. This experiment demonstrates the effectiveness of the pulse oximeter in detecting and amplifying small pulse signals to estimate arterial he-

** Barrington KJ, Ryan CA, Finer NN: Pulse oximetry during hemorrhagic hypotension and cardiopulmonary resuscitation in the rabbit. J Crit Care 1:242–246, 1986.

†† Tremper KK, Hufstedler S, Zaccari J, Schaefer R: Pulse oximetry and transcutaneous P_{O_2} during hemorrhagic and normotensive shock in dogs. ANESTHESIOLOGY 61(3A):A163, 1984.

moglobin saturation. This experimental model is not analogous to clinical shock, for as the blood pressure cuff is progressively inflated, there is a progressive increase in the venous blood volume. Theoretically, this increase in venous blood should not influence the pulse oximeter because it is nonpulsatile.

Patient motion (large AC/DC signal) may be the most difficult artifact to eliminate. Motion artifact rarely causes difficulties in the operating room, but in the recovery room and intensive care unit it can make the pulse oximeter nearly useless. Engineers have tried several approaches to this problem, beginning with the signal averaging time. If the device averages its measurements over a longer time period, the effect of an intermittent artifact will be lessened. This also slows the response time to an acute change in SaO_2. Most pulse oximeters allow the user to select one of several time averaging modes. In addition, the designer can use sophisticated algorithms to identify and reject spurious signals. These algorithms may assess the AC-to-DC signal ratio, or they may check the validity of the saturation estimate by calculating its rate of change. For example, if the saturation estimate changes from 95% to 50% in one-tenth of a second, this sudden change may not be averaged into the displayed SpO_2, or it may be given a lower weighting factor.[11] As stated earlier, these artifact rejection schemes may also affect the accuracy and response time of the pulse oximeter.

Accuracy and Response

There are both technologic and physiologic limitations to the accuracy of a pulse oximeter. The SpO_2 value is only as accurate as the empirical calibration curve programmed into the device, which, in turn, is only as accurate as the *in vitro* laboratory oximeter used to generate it. The Instrumentation Laboratories model 282 Co-oximeter claims an accuracy of ±1% for fractional saturation (±2 standard deviations) when the *p*H is 7.0–7.4, MetHb is 0–10%, and the total hemoglobin is 12–16 grams per deciliter.‡‡

Before reviewing studies that are intended to determine pulse oximeter accuracy, we should discuss some problems in the statistical interpretation of accuracy data. These studies are referred to by statisticians as "methods-comparison studies."[33–35] A methods-comparison study uses two methods to measure the same variable. One method is usually a new technique (in this case, pulse oximetry), and the other is a "gold standard" (in this case, *in vitro* saturation measurements from arterial blood samples). Bearing in mind that both methods have uncertainty, we wish to know what error to expect if the new method is compared to the standard. In the medical literature, the data analysis usually includes a correlation coefficient (r) with a *P* value, and a linear regression slope and intercept. Unfortunately, this is not the most informative statistical analysis for methods-comparison studies.[33,34] The correlation coefficient is not a measure of agreement; it is a measure of association. We know that pulse oximeter SpO_2 values and SaO_2 values are highly associated, and we therefore expect a correlation coefficient that is significant. This does not tell us whether one measure of saturation can be used in place of the other, or what degree of confidence we should have in the new measure.

As an alternative, Altman recommends calculating the mean and standard deviation of the difference between the two methods of measurement.[33,34] The mean of the difference is called the "bias" and the standard deviation is often referred to as the "precision." The bias will show a systematic overestimate or underestimate of one method relative to the other, while the precision will represent the variability or "random error." If these systematic and random errors are clinically acceptable, then one method can be replaced by the other.

Unfortunately, in the pulse oximetry literature, many authors provide only correlation coefficient and linear regression analysis. It is difficult to compare their results in terms of measurement accuracy without bias and precision values. Most manufacturers claim that their pulse oximeters are accurate to within ±2% (SD) from 70% to 100% saturation and ±3% (SD) from 50% to 70% saturation, with no specified accuracy below 50% saturation. This implies that, for SaO_2 above 70%, approximately 68% of the data will fall within ±2% of a line of identity, and 95% of the data will fall within ±4% (±2 SD).

In reviewing the pulse oximetry literature, two additional points should be kept in mind. First, some of these studies were carried out in healthy adult volunteer subjects, while others were conducted on patients in a variety of clinical settings. The studies using healthy volunteers were performed under optimal conditions, while the clinical studies were done in a variety of less than optimal conditions. Second, since these devices are empirically calibrated, the algorithm programmed into each oximeter undergoes a series of revisions that affect the accuracy and response characteristics. Table 1 summarizes the results from twelve studies: five in adult volunteers, three in adult patients, and two each in pediatric and neonatal patients. The data from each of these studies were analyzed differently by the authors. Most consistently presented are correlation coefficients and regression slopes and intercepts. This is sometimes accompanied by a standard error of the estimate (SEE or S_{yx}), which is the standard deviation of y values about the regression line.

Experimental studies on early models of the Nellcor

‡‡ IL282 Operators Manual #79282 Instrumentation Laboratories, Lexington, Massachusetts. Section 10, page 1, 1978.

TABLE 1. Pulse Oximeter Experimental and Clinical Accuracy Data

Reference	Manufacturer	r	s	i	N	SEE% (Syx)	Range % high-low	Bias ± Prec.
Experimental Studies in Adult Volunteers								
Yelderman[15]	N-100	.98	1.03	−2.33	79	1.83	98-65	
Chapman[36]	Biox II	.96	.79	17.9	117	2.72	100-54	
Kagle[38]	Ohmeda 3700 (XJ1)	.99	.96	4.59	48	2.7*	99-60	
	N-100	.99	.96	5.34	48	2.7*	99-60	
Severinghaus[37]	N-100				60		70-40	6.6 ± 10.8
	N-200				60		70-40	−4.5 ± 8.2
	Ohmeda 3700				60		70-40	2.7 ± 5.8
	CR (.28)				60		70-40	1.4 ± 5.9
	PC (1600)				60		70-40	0.0 ± 3.5
	NO (3.3)				120		70-40	1.1 ± 5.4
	MQ (7)				36		70-40	−2.9 ± 5.2
	Datex				59		70-40	−1.6 ± 5.4
Nickerson[39]	Ohmeda 3700				165		100-65	−2.6 ± 2.1
	CR				165		100-65	−1.0 ± 2.8
	N-100				165		100-65	−0.4 ± 1.7
	NO				165		100-65	−1.0 ± 1.6
Clinical Studies in Adult Patients								
Tremper[27]†	Biox III	.57	.93	5.22	383	3.09	100-81	1.4 ± 3.1
Mihn[40]	N-100	.96	.97	1.51	131		100-56	
Cecil[41]	Ohmeda 3700	.83	.95	.42	333		100-62	−.31 ± 2.44
	N-100	.80	.78	21.2	330		100-62	0.59 ± 3.02
Clinical Studies in Pediatric Patients								
Fait[42]	N-100	.89	1.05	−6.56	192		100-70	
Boxer[43]	N-100	.95	1.01	0.15	108		95-35	−.87 ± 3.7
Clinical Studies in Neonatal Patients								
Mok[44]	N-100	.84	.65	27.8	27		100-43	1.4
Durand[45]		.86	.68	29.6	108	2	100-78	−.2 ± 2.5

r, s, and i are linear regression correlation coefficients, slopes, and intercepts, respectively; N = number of data pairs; SEE (Syx) is the standard error of the estimate. Bias is the mean difference between SpO_2 and SaO_2; Prec. is the standard deviation of the differences. All manufacturers specified accuracy are similar, 1 SD = ±2%, 100% to 70–80%, 1 SD = ±3%, 70–80% to 50%, and unspecified < 50%. Manufacturers: N-100 and N-200 (Nellcor); Biox II, Biox III, and Ohmeda 3700 (Ohmeda); CR (Criticon); PC 1600 (Physio Control); NO (Novametrix); MQ (Marquest); and Datex. The software revision is in parenthesis following the manufacturer abbreviation when this information was provided in the referenced study. (Nellcor N100 Technical Manual. Nellcor Corporation, Hayward, CA; Ohmeda 3700 Pulse Oximeter Technical Manual. Ohmeda Division of BOC, Boulder, CO; Novametrix 500 Pulse Oximeter Technical Manual. Novametrix Medical Equipment, Wallingford, CT.)

* These values of Syx are determined from the authors 99% confidence intervals.[38]

† The SpO_2 data were collected in patients with pulmonary artery catheters for simultaneous cardiac output determinations. Therefore, these patients were probably more critically ill than those in the other studies.[27]

N100 and the Ohmeda Biox II showed good agreement under steady-state conditions when the saturation was 75% or greater (table 1). Chapman *et al.* noted that in this SaO_2 range the bias was only 0.09%.[36] For SaO_2 less than 75%, they found increasing overestimation by the pulse oximeter. Between 50% and 60% SaO_2, there was a positive bias of 11.2%, whereas between 70% and 75%, the bias was 3.88%.

Two recent studies are of particular interest because they evaluated pulse oximeter accuracy during deep desaturation and also measured response times to rapid desaturation and resaturation.[37,38] Both studies revealed errors in some manufacturers' calibration algorithms. This prompted these manufacturers to revise their algorithms and their devices were subsequently reevaluated. This emphasizes again the importance of specifying the software revision employed in any pulse oximeter study. Unfortunately, most reports do not specify the software revision (table 1). Kagle *et al.* evaluated the Ohmeda 3700 (XJ1 software) and the Nellcor N100 in a volunteer study and found 99% prediction limits of ±8% over a saturation range of 60–100%. Since 99% prediction limits are ±3 SD, this implies a standard deviation of ±2.7%, not far from manufacturers specifications.[38] These authors also measured the time for 50% recovery of resaturation from a hypoxic state. With the pulse oximeter set on the "fast" (3 s) averaging mode, the ear probe showed resaturation more quickly than the finger probe (6 s *versus* 24 s).[38]

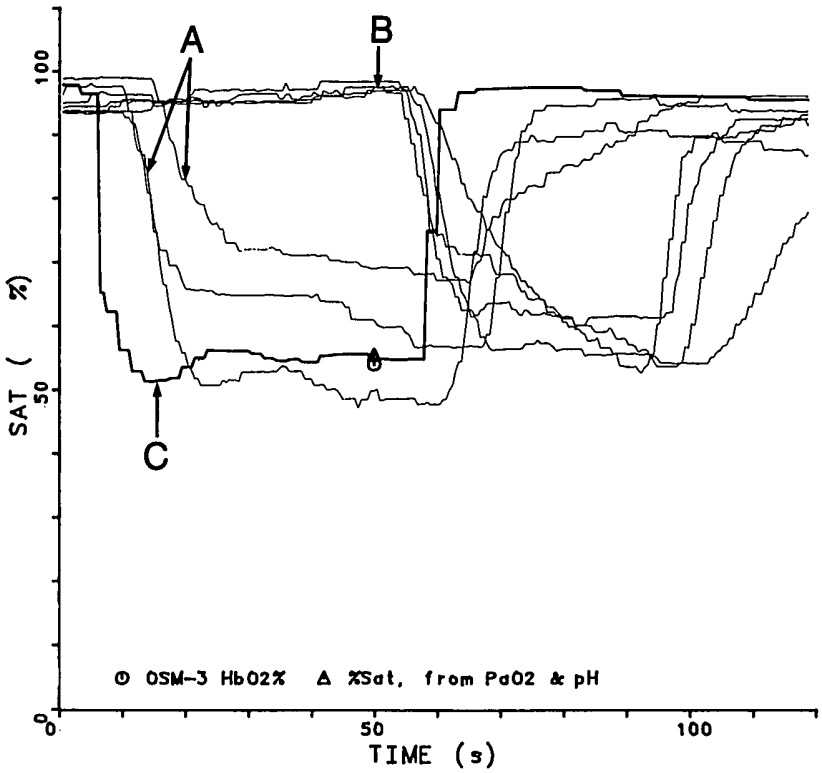

FIG. 5. The above tracings show data from seven pulse oximeters: three ear probes (A), and four finger probes (B), during deep desaturation in adult volunteers. Line labeled C is saturation calculated from expired oxygen tension. Note the rapid but variable response of the ear probes A lagging only 10 s behind the expired oxygen values, whereas the finger probes B show a nearly 50-s lag time in this volunteer. Adapted from Severinghaus JW, Naifeh KH: Accuracy of response of six pulse oximeters to profound hypoxia. ANESTHESIOLOGY 67:553, 1987, with permission.

Severinghaus and Naifeh published an interesting volunteer study comparing seven different pulse oximeters during severe desaturation.[37] They also measured response times for both ear and finger probe desaturation and resaturation. This study did not determine accuracy over a range of steady-state saturations, but rather during a sudden, brief desaturation to an SaO_2 of 40–70% (table 1; fig. 5). The authors noted significant variations in bias and precision among manufacturers as well as among subjects. The bias varied from +13% to −9%, with a precision as high as 16%. They also found that ear sensors were usually more accurate than finger sensors. This difference in accuracy could be a result of the unsteady nature of this experiment (fig. 5). The SpO_2 response times were again much faster for ear probes than for finger probes. The $T_{1/2}$ for the ear probe during desaturation ranged from 9.6 to 19.8 s, while for the finger probes it ranged from 24 to 35.1 s. This differing response time is presumably due to different perfusion time constants for the ear and finger circulation. The response to resaturation was faster than to desaturation, as shown in figure 5. One problem with this study that may limit the comparison of the devices is that the signal averaging times of the monitors were not the same. This would affect their response time to transients, and may also affect their accuracy during brief, deep desaturation. As seen in figure 5, SpO_2 values from the finger probes were still falling when the expired oxygen level and ear sensor SpO_2 had already shown resaturation. Therefore, some oximeters may have not reached equilibrium at steady-state desaturated SpO_2 values due to their longer averaging times.

The most recent volunteer study examined the accuracy of four pulse oximeters over a range of saturation from 65 to 100% (table 1).[39] This study also compared the results of three bench oximeters and SaO_2 calculated from a blood gas analyzer using the multiwavelength IL-282 Co-oximeter as the reference. Two of the bench oximeters (which employed two wavelengths) yielded bias and precision values of −4.2 ± 2.5% and +1.8 ± 0.7%.[39] The calculated SaO_2 values from the blood gas machine were of similar accuracy: −1.8 ± 2.4%. The accuracies of the pulse oximeters compared favorably to these values (table 1).[39]

Among the clinical studies on adult patients, Tremper *et al.* found a low correlation coefficient of .57, but a bias ± precision of 1.4 ± 3.1%.†† These bias and precision values are similar to those of volunteer studies and the two other adult clinical studies presented in table 1. The clinical studies of Mihm *et al.* and Cecil *et al.* obtained r values of .8 to .9, which were higher than those of Tremper due to the wider saturation range over which the data were collected. Comparing these results demonstrates how the correlation coefficient alone can be a misleading index of accuracy in methods-comparison studies.

The accuracy of pulse oximeters is impressive, considering the many possible sources of error. We should remember that the specified uncertainty of ±2% to 3% is for one SD, or a 68% confidence interval. If we desire

95% (2 SD) or 99% (3 SD) confidence, then the uncertainty is two or three times as large, respectively.

Clinical Consequences of Pulse Oximetry

As any new technique becomes a standard of care, there is a time window during which it is ethically feasible to perform randomized, controlled studies of its effectiveness. A recent clinical study by Cote' *et al.* has confirmed the necessity of SpO_2 monitoring during pediatric anesthesia.[46] One hundred and fifty-two patients were continuously monitored with SpO_2 during anesthesia. In half of these patients, the SpO_2 data were "unavailable" to the anesthetic team. A major desaturation event was defined as $SpO_2 \leq 85\%$ for 30 s or longer. There were 24 major events in 76 cases when SpO_2 data were "unavailable," and only 11 when the SpO_2 data were "available." The majority of these events occurred in patients $\leq$ 2 yr of age in both groups. Smaller pediatric patients have a greater tendency to desaturate due to their relatively high oxygen consumption, smaller functional residual capacity, and possible fetal circulatory pattern.[46] Raemer *et al.* blindly collected SpO_2 data from 108 outpatients during gynecologic surgery.[47] They found episodes of moderate desaturation ($SpO_2 \leq 90\%$) in 10% of the cases and severe hypoxemia ($SpO_2 \leq 85\%$) in 5% of the cases. Under current recommended standards for anesthetic monitoring, it may be difficult to conduct further controlled studies on intraoperative SpO_2 monitoring.

Monitoring during transport to the recovery room has also been examined in children and adults.[48,49] Pullerits *et al.* monitored 71 healthy pediatric patients during transport and found that 28.1% had SpO_2 values $\leq 90\%$, while only 45% of these desaturated patients had observable cyanosis.[55] In a similar study of adult patients, Tyler *et al.* found that 35% had SpO_2 values $\leq 90\%$, and 12% had SpO_2 falls to 85% or less.[49] Both studies conclude that due to the high incidence of desaturation and the inability to clinically recognize it, all patients should receive supplemental oxygen during transport from the operating room to the recovery room.[48,49]

The oxygenation of adult and pediatric patients in the recovery room has been evaluated with interesting results.[50,51] Soliman *et al.* compared SpO_2 to a postanesthesia recovery score in children.[50] The postanesthesia recovery (PAR) score is a system based on motor activity, respiratory effort, blood pressure, consciousness, and color. An $SpO_2 \geq 95\%$ was considered adequate oxygenation for a healthy pediatric patient. They found no correlation between the PAR score and the patients' oxygenation.[50] They concluded that pediatric patients in the recovery room should be monitored continuously with pulse oximetry or at least treated with supplemental oxygen regardless of their apparent wakefulness, and that an SpO_2 value should be included among the recovery room discharge criteria. Morris *et al.* studied 241 adult patients in the recovery room, measuring SpO_2 values upon arrival, 5 min after arrival, 30 min after arrival, and just prior to discharge.[51] The recovery room personnel were blinded to the SpO_2 data. Of the 149 inpatients studied, 14% had episodes of desaturation to below 90%. As might be expected, the factors associated with desaturation were obesity, extensive surgery, age, and ASA physical status. Most surprising is the fact that more patients were found to be hypoxemic at the time of discharge than at any of the other measurement times.[51] These results demonstrate our present lack of knowledge as to what saturation levels imply immediate danger or a poor prognosis in postoperative patients under various clinical circumstances.

In examining the clinical consequences of pulse oximetry, we must be aware of the pulse oximeter's limitations. Arterial oxygen tension can vary over a wide range during general anesthesia, but SpO_2 will reflect none of this variation until desaturation occurs as Pa_{O_2} decreases below 100 mmHg. The pulse oximeter is effectively a sentry standing at the edge of the "cliff" of desaturation.

This paper is not intended to be an exhaustive survey of the literature on pulse oximetry. It is a brief review of the physics and physiology on which the technique is based, the technical problems with SpO_2 measurements, and selected clinical studies involving the technique. Pulse oximetry has made a dramatic impact on anesthesia monitoring over the past few years. In a survey conducted by the nation's largest medical malpractice underwriter, pulse oximetry was used in every anesthetic by 17.8% of the surveyed anesthesia providers in 1986, while that percentage increased to greater than 60% by 1987.§§ The ultimate effect on patient morbidity and mortality is yet to be determined.§§ Considering that the most common cause of anesthesia-related preventable deaths is hypoxia, we expect routine use of pulse oximetry to prove to be of significant benefit.[52,53]

The authors wish to thank Jonas A. Pologe, BSEE (Manager of Research, Ohmeda/Biox, Boulder, Colorado), for his advice and Jenny Mace and Virginia Marana for their technical assistance in the preparation of this manuscript.

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