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Abstracts:

Takuo Aoyagi: Discovery of Pulse Oximetry

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In the 1930s and 1940s, photo cells permitted German, English, and American physiologists to construct ear oximeters with red and infrared light, requiring calibration. In 1940 Squire recognized that changes of red and infrared light transmission caused by pneumatic tissue compression permitted saturation to be computed. In 1949 Wood used this idea to compute absolute saturation continuously from the ratios of optical density changes with pressure in an ear oximeter. In 1972 Takuo Aoyagi, an electrical engineer at Nihon Kohden company in Tokyo, was interested in measuring cardiac output noninvasively by the dye dilution method using a commercially available ear oximeter. He balanced the red and infrared signals to cancel the pulse noise which prevented measuring the dye washout accurately. He discovered that changes of oxygen saturation voided his pulse cancellation. He then realized that these pulsatile changes could be used to compute saturation from the ratio of ratios of pulse changes in the red and infrared. His ideas, equations and instrument were adapted, improved and successfully marketed by Minolta about 1978, stimulating other firms to further improve and market pulse oximeters worldwide in the mid 1980s. Dr. Aoyagi and associates provided a detailed history for this paper.

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OXIMETRY HISTORY

Karl von Vierordt (Tübingen, 1876) measured the rate of spectral changes of light penetrating tissue when circulation was interrupted. His work was ignored until Ludwig Nicolai (Göttingen, 1931) repeated that study. Nicolai's device measured red light transmission through a hand. In 1939 Karl Matthes in Leipzig introduced ear oximetry, counterbalancing red and infrared light. J. R. Squire (London, 1940) was the first to realize that the differences of transmission of red and infrared light before and after expelling the blood from the web of the hand with a pressure cuff was a function of saturation (1). Pulse oximetry may be regarded as a sequel to Squire's device and idea, using pulsatile changes in tissue blood volume instead of compression vascular collapse.

Oximetry development was stimulated during WW II in an effort to warn military pilots of dangerous hypoxia. Glen Millikan (1906–1947) developed a lightweight red and infrared ear oximeter in 1942 for which he coined the word "oximeter" (2).

Earl Wood (Mayo Clinic, 1949) and his PhD student, J. E. Geraci, modified the Millikan ear piece by incorporating Squire's pneumatic cuff. Wood extended and mathematically developed the ideas of Squire, plotting the ratio of the ratio of red to infrared light optical ear density produced by compression and reperfusion as a unique function of saturation (3). After setting gains with the bloodless ear, Wood divided the decreased red signal by the decreased infrared signal to obtain saturation without calibration. However, in practice, users often set the signal to 100% while the subject breathed oxygen.

AOYAGI AND HIS PULSE OXIMETER

Takuo Aoyagi was born on February 14, 1936, in Niigata Prefecture, Japan, and graduated in 1958 from the Faculty of Engineering at Niigata University with a degree in electrical engineering. Initially he worked at Shimadzu, a scientific instrumentation company.

In February 1971 he joined the Research Division of Nihon Kohden Corporation. Initially his dream was to make a sensor of blood oxygen saturation to signal the need for artificial ventilation, and to accomplish this he studied the oximetry literature. Impressed with Wood's plot of red and infrared light hemoglobin density (3), he obtained and studied a Japanese version (Erma) of Wood's oximeter earpiece. He concluded that an ear oximeter could be used to record a dye dilution curve, but would require calibration with a blood sample. Because arterial pulsatile "noise" prevented accurate recording of the dye clearance, he invented a method to eliminate this noise, which led to his discovery. He wrote of this work in 2003 (4):

"These [variations due to the pulse] prevented accurate extrapolation of the down-slope of the dye curve after recirculation begins. I investigated this problem mathematically using the Lambert-Beer law. Then I conceived the idea of eliminating the pulsation

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by computing the ratio of optical densities of the two wavelengths. This supposition was proved workable by experiments."

The Key Idea: The Ratio of Ratios

While testing this way of canceling out the pulsations in the ear dye densitometer, Aoyagi observed that, by holding his breath, a decrease of oxygen saturation reintroduced pulsatile waves by changing the ratio of densities at the two wavelengths. This led him to predict that this artifact might be used to measure arterial oxygen saturation. He continues:

"At this point I realized that both the pulsating portion and non-pulsating portion of optical densities of the blood in tissue must have the same information of blood color. And I imagined as follows:

(1) If the optical density of the pulsating portion was measured with two appropriate wavelengths and their ratio was obtained, the result must be same as Wood's ratio.
(2) In this method the arterial blood is selectively measured and the venous blood does not affect the measurement. Therefore the probe site is not restricted to the ear.
(3) In this method the reference (comparable to the blanched ear reference) is set with each pulse.

Therefore a probe shift of location, or motion introduces only a brief artifact, before quickly returning to normal measurement. This was my conception of the pulse oximeter principle in December, 1972."

He confirmed both theoretically and experimentally the validity of Wood's plot of the density ratios. Aoyagi called the ratio of ratios ϕ:

$$Spo_2 = f\phi$$

where

$$\phi = (AC_{red}/DC_{red})/(AC_{IR}/DC_{IR})$$

where AC and DC symbolize the pulsatile and non-pulsatile components of the transmitted light.

Greatness in science often, as here, comes from the well-prepared mind turning a chance observation into a major discovery. "One man's noise is another man's signal" commented the respiratory physiologist Jere Mead half a century ago.

Development of the Oximeter

Aoyagi tested various wavelengths and methods of implementing the pulse oximetry idea. He selected the 630-nm wavelength, at which red light absorption was most sensitive to oxygen saturation, and he balanced this against a 900-nm infrared wavelength, which is not absorbed by dye. Indo-cyanine green dye was selected for cardiac output measurement because its absorption peaks at 805 nm, the isobestic point where hemoglobin and oxyhemoglobin have equal absorption, making dye dilution curves independent of saturation. Aoyagi noted that blood optical density at 900-nm decreased with desaturation, resulting in a larger signal than provided by ratios at 630 and 805 nm.

In early 1973, Aoyagi's supervisor, Y. Sugiyama, told Dr. Susumu Nakajima, a surgeon then working at the Sapporo Minami National Sanatorium, of Aoyagi's pulse oximetry invention. Nakajima, understanding that the method was a secret to be kept, placed an order with Nihon Kohden for the as-yet-undeveloped apparatus.

Aoyagi wrote (4):

"I assigned Mr. Michio Kishi chief of this project. For this pilot model, components of the dye densitometer were used. The light source was a small tungsten lamp. The transmitted light was divided into two and each [beam] was received with combination of an interference filter and a phototransistor. I used wavelengths of 630nm and 900nm. I selected 900 nm to avoid interference by [the dye] ICG. From the transmitted light, pulsation amplitude 'AC' and the total 'DC' were obtained and the ratio AC/DC was calculated. This AC/DC ratio was obtained at the two wavelengths and their ratio, phi (ϕ) was calculated. This ϕ was expected to correspond to Sao_2."

"For both dye densitometry and pulse oximetry, it was necessary to have a theoretical base of scattering optics.[1] Dr. Kazuo Shibata of Tokyo Institute of Technology had been studying for many years methods of measurement of pigments in plants *in vivo*. I read his papers and consulted with him regarding the state-of-the-art. The only way to decrease the effect of error sources was to use one or two scattering plates. This method was called the "opal-glass method". We adopted this method. By late 1973 the oximeter was ready and clinical evaluation was conducted in Sapporo."

Disclosure of the Invention

Aoyagi reported his discovery of pulse oximetry to the Japanese Society of Medical Electronics and Biologic Engineering (MEBE) on April 26, 1974 (5) and published with his many collaborators (6). On March 29, 1974, a patent application titled "Apparatus for Photometric Blood Analysis" was submitted to the Japanese Patent Office by the Nihon Kohden Corporation, naming Aoyagi and Kishi as inventors. This patent was publicly disclosed on October 9, 1975, and published on August 2, 1978 (No. 53-26437); Patent 947714 was granted on April 20, 1979.

Competitor

On April 24, 1974, two days before the MEBE meeting, a patent application also describing the use of the arterial pulse for oximetry was submitted by Masaichiro Konishi and Akio Yamanishi, named as

[1]The experimental ratio of ratios deviates from theory due largely to scattering by tissue. Aoyagi has sought and identified ways of minimizing this error.

inventors working at the Minolta Camera Company. This remarkable simultaneity of discovery led me, in reviewing this history, to inquire about the possibility that the secret was discovered in Aoyagi's submitted abstract in advance of the meeting. Aoyagi wrote (personal communication, September, 2006):

"For presentation at MEBE, a preliminary abstract had to be submitted in the fall. In October, 1973, I submitted an application for a presentation, with a short explanation of the pulse oximeter principle. Many referees checked them and perhaps almost all of them were allowed to submit abstracts. My preliminary abstract was very short, but the [pulse oximeter] idea was written in it.[2] The application was accepted." In January 1974, Aoyagi submitted to MEBE the complete abstract describing the invention.

Aoyagi continued:

"Yamanishi is familiar to me because [several years later, and while employed by their different companies] we two worked together to try to make a pulse oximeter calibrator using real blood, at the request of Dr. K. Miyasaka (then head of anesthesia at National Children's Hospital, Tokyo). Recently Yamanishi wrote a historical story of the pulse oximeter for the Japanese Society of Medical Instrumentation and it was published (7)."

In November 2006, at my request, Yamanishi shared his records and memories of these events with me [personal communication]. In the Fall of 1973, he was given a copy of Wood's oximeter chapter (3) by his supervisor Konishi. Yamanishi had been interested in the operation of blanching and refilling the blood in the earlobe. He had been studying photo plethysmography for a year, particularly the work of Takeda et al. of Nippon Medical School (Tokyo) (8). He was aware of the effect on optical signal ratios of change of thickness of arterial blood in the tissue. In his 2005 review of events of 30 years past (7) he wrote (translation by Aoyagi): "In January, 1974, Yamanishi made up an idea of pulse oximeter and handed to a person in charge of patent saying 'This is big invention.'"[3]

He thought that combining the idea of varying tissue blood volume with the larger signal of the finger would permit measurement of oxygen saturation. In April 1974 shortly before the 13th Conference of MEBE, Yamanishi noticed Aoyagi's abstract on the pulse oximeter. He was surprised that his own group [Minolta] had only developed the theory, whereas Aoyagi et al. had already constructed an experimental model. Urged by Konishi and Yamanishi, Minolta's patent section submitted the document to the Japanese patent office on 24th April, hoping to establish their claim before more information was disclosed in the conference. The Japanese Patent Office rejected Konishi's patent application in 1982. In the United States, Minolta applied for and obtained patent protection with limited effect, being based on a subsequent Minolta patent in Japan.

Aoyagi's prototype pulse oximeter was tested in conjunction with Dr. Nakajima in Sapporo on September 6 and 7, 1973 and by Nakajima and his associates on February 5 to 7, 1974 (9). It used an earpiece with incandescent light, filters, and photo transistors. However, Nihon Kohden did not continue to develop or market this instrument and made no effort to patent it abroad. Aoyagi was transferred to a post as assistant manager in the patient monitoring division of Nihon Kohden in September of 1975, and the research and development of the pulse oximeter was assigned to another worker. The pulse oximeter subsequently was marketed, but its performance was not satisfactory.

The Minolta Company developed Yamanishi's oximeter concept using a fingertip probe to take advantage of the greater pulse amplitude. Light sources and signals were conducted through fiberoptic cables to and from the instrument, as was done in the Shaw-Hewlett Packard multiwavelength ear oximeter. Minolta's device was marketed in 1977 as the Oximet MET-1471. Its response to hypoxia was reported to be linear and accurate to within 5% by Suzukawa et al. in 1978 (10) and Yoshiya et al. in 1980 (11). Nakajima and associates used it clinically in 1979 (12). However, when studied at Stanford in 1980 by Sarnquist et al. (13) a Minolta model 101 [identical to Oximet MET-1471] seriously underestimated the severity of hypoxia: At 50% actual Sao_2 it read about 70%. Yamanishi wrote me (personal communication, 2006): "The Sarnquist data was the very important trigger for us to improve the accuracy of our pulse oximeter." In 1984, Y. Shimada (then anesthetist of Osaka University, now professor of Nagoya University) with Minolta's K. Hamaguri, I. Yoshiya, and N. Oka (14) published data using a Minolta Oximet MET-1471 that agreed with Sarnquist's evidence of under-reporting the degree of desaturation. In this paper, this group developed perhaps the first theory of pulse oximetry that included scattering effects by blood cells.

Aoyagi wrote (personal communication):

"Although it was a rather too simple a theoretical formula, it encouraged me to build up my theoretical formula. There was a big difference between Minolta and Nihon Kohden. In Nihon Kohden the idea of pulse oximeter was denied by the person in charge of optical plethysmography. After my shift to another position, Nihon Kohden made no improvement in pulse oximeter technology until world-wide spread of Nellcor's oximeters. On the contrary, Minolta made up a highly accurate instrument using their excellent optical technology, and later even made a model change before Nellcor. I appreciate Minolta. Without their recognition of idea of pulse oximeter, the idea might be buried."

[2]Konishi was on the MEBE board and may have seen Aoyagi's notes.

[3]This was, as far as I know, Yamanishi's first mention in print (7) that he had had the idea in January 1974 of using the arterial pulse to generate the AD/DC variations.

Finally, in September 1985, Aoyagi was permitted to resume research and development of his pulse oximeter. His subsequent work has focused on the mechanism causing the nonlinearity of the Beer's law relationship of light transmission to saturation. He developed the theoretic background for both pulse oximetry and later for use of multiple wavelengths for other clinically useful purposes. His pulse spectrophotometer permits determination of plasma volume, hepatic blood flow and cardiac output after dye injection.

Aoyagi was granted the degree of Doctor of Philosophy in Engineering at Tokyo University on December 1993. He was awarded two prizes in 2002. The "Social" award was given for research other than on anesthesiology by the Japanese Society of Anesthesiologists. The Purple Ribbon Medal was given him by the Emperor of Japan for contributions to sciences and arts. Nihon Kohden was then persuaded to allow him to continue his research after retirement.

CONCLUSION

Introduction of pulse oximetry coincided with a 90% reduction in anesthesia-related fatalities. Takuo Aoyagi's invention was serendipitous. Although he could use the infrared signal to cancel pulsatile "noise" in the dye decay optical signal, hypoxic desaturation spoiled the smooth dye curve. In that noise, he recognized a useful signal—oximetry—because his mind was well prepared to understand what he saw happen. The process of turning his insight into more accurate, convenient and inexpensive saturation monitors still continues in dozens of laboratories and firms, while he continues to innovate.

Author's Postscript

In 1985, I was asked by Professor J. Payne to present the history of pulse oximetry to a meeting in the United Kingdom, later published (15). Using only published literature, I made serious errors because the original papers in Japanese were not authored by the inventor, but by surgeons. After seeing my paper, my former collaborator Professor Yoshi Honda, MD (1926–2003) of the Department of Physiology of Chiba University investigated this discovery and introduced me to the inventor, Takuo Aoyagi, Ph.D. Honda and I published corrections of this story in 1987 (16,17). I am indebted to Dr. Aoyagi and Akio Yamanishi (Minolta) for providing additional background described here related to the invention of pulse oximetry.

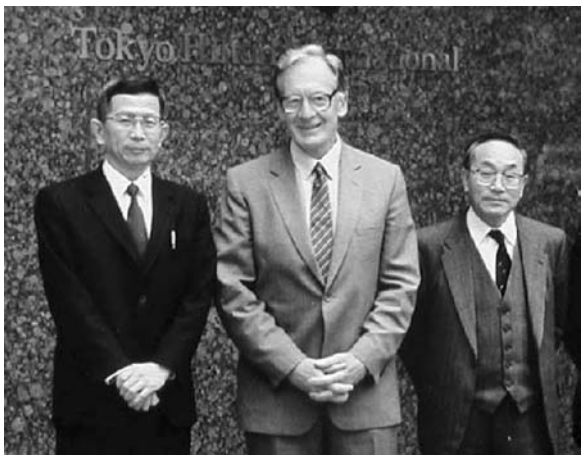

Figure 1. Takuo Aoyagi, John Severinghaus, and Yoshiyuki Honda, 1987.

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Misconceptions in Reporting Oxygen Saturation

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BACKGROUND: We describe some misconceptions that have become common practice in reporting blood gas and cooximetry results. In 1980, oxygen saturation was incorrectly redefined in a report of a new instrument for analysis of hemoglobin (Hb) derivatives. Oxygen saturation (sO_2) was redefined as the ratio of oxyhemoglobin (O_2Hb) to total Hb instead of the ratio of O_2Hb to active Hb (O_2Hb + desoxyhemoglobin). In addition, the new terms "functional saturation" and "fractional saturation" were introduced. Since the new parameter was implemented in a widely used cooximeter, its use is now widespread and has caused misunderstandings.

METHODS: In this report, we review the development of the definitions and measurements of sO_2 and related quantities and contend that the misconceptions should be resolved by standardizing instrument read-outs and clinical reports, so that sO_2, defined as the ratio of O_2Hb to active Hb, should replace FO_2Hb and be reported along with the total Hb concentration and the common dyshemoglobin fractions (%CO-Hb and % methemoglobin [metHb]).

RESULTS: The redefinition of sO_2 as the $\%O_2Hb$ or FO_2Hb did not address the confusion that might result from interchanging these two often-similar but different terms. The term fractional saturation is an inappropriate terminology and lacks clear physiological meaning. We see frequent cases of confusion: (a) the difference between the sO_2 in pulse oximetry and the FO_2Hb in cooximetry is called the "pulse oximeter gap;" (b) sO_2results are described as "method dependent;" and (c) reference ranges for these terms are substituted.

CONCLUSIONS: Although either parameter could be used by clinicians who fully understand the relatively simple difference between these parameters, we find clear evidence that there is widespread confusion of these terms, even among experts in the field. Standardization of the reporting format would help, and instrument manufacturers could contribute by standardizing the reporting format for cooximetry results.

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We call attention to a misunderstanding of terms that has crept into common practice over the years in reporting blood gas and cooximetry results. It began in 1980 with the introduction of an incorrect redefinition of O_2 saturation (sO_2) in a report of a new instrument for analysis of hemoglobin (Hb) derivatives (1). Oxygen saturation (sO_2) was redefined as the ratio of oxyhemoglobin (O_2Hb) to total Hb, instead of the ratio of O_2Hb to active Hb (O_2Hb + desoxyhemoglobin [HHb]). This definition was implemented in the computer program of the instrument and its successors, which were introduced into the market. No arguments were given for this change from the original definition on the sound fundamental work of Christian Bohr around 1900 and presented in textbooks of physiology. The report (1) simply stated, "Defining saturation in terms of all Hb species present gives a more exact and meaningful interpretation of the data." Although it was almost immediately noted that significant misunderstandings would result (2), this did not provoke either a discussion or a retraction of the new definition.

The interchanging of these two similar but different definitions of sO_2 has led to confusion between the saturation reported by pulse oximetry (sO_2) and that reported by many blood gas analyzers (FO_2Hb). This has fostered the idea that the definition of sO_2 is instrument-dependent, and suggested that there are two kinds of saturation (3). These, now widespread, misconceptions have become entrenched in the clinical literature and have occasionally confused the proper clinical interpretation.

For example, a recent guideline for treating carbon monoxide (CO) poisoning, published in the Netherlands (4), stated that under these circumstances transcutaneous oximetry is unreliable, because of a consistent overestimation of sO_2 by the pulse oximeter. Although the statement was accompanied by two references (5,6), it was based on the incorrect assumptions that the sO_2 is

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decreased by the presence of carboxyhemoglobin (COHb) in the blood, and that the pulse oximeter would somehow detect the presence of COHb. These are erroneous assumptions because: 1) the calculation of sO_2 is independent of COHb, 2) clinically sO_2 does not decrease in CO poisoning because there is no noticeable decrease in pO_2, and 3) the pulse oximeter is, at the wavelengths used, virtually insensitive to COHb (7).

We believe that the O_2-carrying properties of the blood can be clearly described using three well-defined quantities: O_2 capacity (BO_2), sO_2, and O_2 affinity (3). These quantities can be reliably measured in patients and provide useful information for the treatment of impending hypoxia.

Although the quantities pertaining to the O_2-carrying properties of blood are explained in most textbooks of physiology, we present here a concise summary of the definitions and measurement of BO_2, sO_2, and affinity. We also explain the relationship between the various methods and show that the definitions are independent of the measuring systems.

DEFINITIONS OF O_2 PARAMETERS AND PHYSIOLOGIC REQUIREMENTS

BO_2

The BO_2 is the maximum amount of Hb-bound O_2 per unit volume of blood. It is expressed in mmol/L or in mL standard temperature and pressure dry (STPD)/L or mL(STPD)/dL. BO_2 is determined by the concentration of active hemoglobin, which may be expressed as either the concentration of O_2Hb + HHb, or the concentration of the total Hb (ctHb) minus the concentration of any dyshemoglobin (c_{dysHb}) present in the blood. dysHbs are Hb derivatives, which have temporarily or permanently lost the capability of reversibly binding O_2 at physiological pO_2 (8). In most patients, COHb and metHb are the major dysHbs.

Hence, when B and c are expressed in mmol/L and the substance concentration of Hb reflects the monomer:

$$BO_2 = c\text{tHb} - c\text{dysHb} \quad (1)$$

when B is expressed in mL(STPD)/L and c in g/L:

$$BO_2 = \beta O_2(c\text{tHb} - c\text{dysHb}) \quad (2)$$

where βO_2 is the volume of O_2 in mL(STPD) that can be bound by 1 g of Hb.

Theoretically, βO_2 = 22394/16114.5 = 1.39 mL/g, where 22,394 is the molar volume of O_2 in mL(STPD), and 16,114.5 is the molar mass of the monomer of human HbA in g (9). This theoretical value has been confirmed experimentally (8).

To satisfy the O_2-consumption requirements of all cells, the O_2-capacity of arterial blood should be high enough to maintain adequate O_2 flow to all cells throughout the capillary bed. We note that the actual O_2 concentration in milliliter O_2 per deciliter blood (minus the small contribution of dissolved O_2) may be calculated with either the sO_2 or the FO_2Hb (fraction of O_2Hb in total Hb, defined in Eq. 7):

$$O_2 \text{ content} = 1.39 \text{ mL/g} \times FO_2Hb \times \text{total Hb}$$

$$= 1.39 \text{ mL/g} \times sO_2 \times (\text{total Hb} - \text{dysHb}) \quad (3)$$

with FO_2Hb and sO_2 in decimal fraction of 1.00, and Hb concentrations in g/dL.

sO_2

The blood sO_2 is defined as the concentration of Hb-bound O_2 divided by the BO_2. This is equivalent to the concentration of O_2Hb divided by the sum of the concentrations O_2Hb and HHb:

$$sO_2 = cO_2(\text{Hb})/BO_2 \quad (4)$$

$$sO_2 = [c\text{tO}_2 - cO_2(\text{free})]/BO_2 \quad (5)$$

$$sO_2 = cO_2Hb/(cO_2Hb + c\text{HHb}) \quad (6)$$

where cO_2(Hb)is the concentration of O_2 bound to Hb, cO_2(free) is the concentration of O_2 dissolved in blood but not bound to any other substance and ctO_2 is the total O_2 concentration in blood. We note that, although there is a conceptual difference between cO_2(Hb)and cO_2Hb, the two quantities are numerically equal when both are expressed in mmol/L.

The arterial sO_2 should be high to maximize O_2 content, so that the blood is almost fully loaded with O_2 as it enters the capillaries.

O_2 Affinity

The O_2 affinity of the blood is usually demonstrated as a graph of the relationship between sO_2 and pO_2, commonly known as the O_2 dissociation curve (ODC). The influence of other quantities on the O_2 affinity is shown by changes in the position and/or shape of the ODC. The O_2 affinity is decreased by factors such as H^+ ion, pCO_2, temperature (T), and 2,3-diphosphoglycerate, and increased by COHb, and metHb. The standard-ODC is the ODC at pH = 7.40, pCO_2 = 5.33 kPa (40 mm Hg), T = 37°C.

The O_2-affinity should be such that Hb reaches almost full saturation in the lungs, yet readily releases O_2 at the relatively lower pO_2 in the tissue capillaries. At a normal mixed venous sO_2 of about 70% at rest, most O_2 is released at a pO_2 of around 5 kPa (37 mm Hg), which is the driving pressure for O_2 diffusion to most tissue cells.

DEVELOPMENT OF O_2 AND Hb MEASUREMENTS

BO_2

During the first half of the 20th century, the standard method for determining BO_2 was by measuring the concentration of total O_2 of a known volume of blood that had been equilibrated with room air, using the manometric method of Van Slyke and Neill (10), after correcting for the freely dissolved O_2. In the

1960s, an internationally standardized method for measuring Hb in blood (11) became generally accepted, and also became the method of choice for the determination of BO_2. Since this method measured the ctHb, a correction for the presence of dysHb had to be included for the correct calculation of BO_2. The common dysHbs, COHb and metHb, were measured by spectrophotometry (12,13), and BO_2 was calculated using Eq. 2. Presently, *c*tHb and *c*dysHb are usually measured by an automated multiwavelength spectrophotometer, commonly referred to as a cooximeter.

sO_2

The classical procedure for measuring sO_2 was the determination of ctO_2 of a blood sample by means of VanSlyke and Neill's manometric method (10), then repeating the measurement after equilibrating the remaining part of the sample with air at room temperature. After calculation of cO_2(free) for the 2 measurements, sO_2 was determined using Eq. 5. Even with the development of photometric procedures, the manometric method long remained the "gold standard."

Among the accurate photometric procedures for measuring sO_2 are many two-wavelength methods that use various combinations of wavelengths, multiple types of cuvettes with different path lengths, and Eq. 6 for calculating sO_2 (12–14). In current clinical practice, blood samples are typically analyzed for sO_2 simultaneously with ct_{Hb} and the concentration of dysHbs (15,16), performed by means of multiwavelength cooximeters capable of analyzing very small samples (14).

A less-reliable method is the calculation of sO_2 from pO_2, pCO_2, and pH on the basis of the standard ODC using a computer program added to a blood gas analyzer. While the calculation works reasonably well in normal blood, erroneous results may be obtained on patients' blood, because of changes in the O_2 affinity of the blood due to factors not accounted for in the computer program.

sO_2 has also been measured continuously *in vivo*. Since the early German devices of the 1930s and Millikan's first oximeter of 1942, several types of oximeters have been developed, using either transmitted or reflected light (14,17–19). Although these methods are fairly accurate and have been used in some physiological and clinical research (20), the procedures are too complicated for routine clinical use. *Ex vivo* methods for measuring sO_2, i.e., in a cuvette connected to an artery or vein, were developed, especially for use during cardiac catheterization (17–20). Currently, point-of-care devices for conveniently determining sO_2 in very small blood samples have largely replaced the use of the more complicated devices.

Introduction of the pulse principle by the Japanese engineer Takuo Aoyagi made noninvasive *in vivo* oximetry suitable for routine clinical application (21,22). A pulse oximeter is a two-wavelength photometer that determines arterial sO_2 (as in Eq. 6) by measuring pulsating light absorption through well-perfused tissue, such as a finger (14,21). The relationship of the pulse oximeter output signal to sO_2 is determined empirically by measurements in healthy volunteers. Therefore, sO_2 can accurately be measured only in the higher sO_2 range. sO_2 values <70% are determined by extrapolation and are less accurate. In addition, very high levels of metHb can affect sO_2 readings.

O_2 Affinity

Since determining a complete ODC is difficult (23) and the standard ODC of normal human blood is reasonably constant (14,24), the determination of one or a few points of the actual ODC of a patient is usually sufficient. Customarily, the pO_2 is determined at an sO_2 of approximately 50%, from which the p_{50} may be determined as a measure of the O_2 affinity (25). After correcting to pH = 7.40, pCO_2 = 5.33 kPa, and T = 37°C, standard-p_{50} is obtained. The corresponding value as read from the normal standard ODC is 3.554 kPa (27 mm Hg) (14).

Relationship of % Difference ($sO_2 - FO_2Hb$) and % dysHbs (*F*COHb + *F*metHb)

Figure 1 shows a graph of the calculated % difference ($sO_2 - FO_2Hb$) versus the % dysHb concentration for FO_2Hb values ranging from 100% down to 70%. These plots show that for FO_2Hb of 95% and above, the % difference ($sO_2 - FO_2Hb$) is almost exactly equal to the combined percent of %COHb + %metHb. At lower F (80%, 70%, etc.), the % difference ($sO_2 - FO_2Hb$) actually becomes slightly less than the sum of %COHb + %metHb, depending on the proportions of deoxyhemoglobin and dysHb. When the % deoxyhemoglobin equals zero (% dysHb + $\%O_2Hb$ = 100%), the % difference ($sO_2 - FO_2Hb$) again equals the % dysHb.

DISCUSSION

We believe the substitution of (cO_2Hb + *c*HHb + *c*dysHb) for (cO_2Hb + *c*HHb) in calculating sO_2 of Hb is fundamentally incorrect. Consequently, some instruments correctly present sO_2 according to Eq. 6, whereas others incorrectly present sO_2 as the fraction of O_2Hb in total Hb (FO_2Hb):

$$FO_2Hb = cO_2Hb/(cO_2Hb + cHHb + c\text{dysHb}) = cO_2Hb/c\text{tHb} \quad (7)$$

VanSlyke's classic manometric method for determining sO_2 defined sO_2 as the ratio of Hb-bound O_2 and O_2-capacity (Eq. 4), with this ratio dependent on pO_2. The relationship between sO_2 and pO_2 in the ODC expresses the ability of Hb to bind and release O_2 as pO_2 changes. Because the influence of the dysHbs upon the O_2-affinity is a secondary effect, analogous

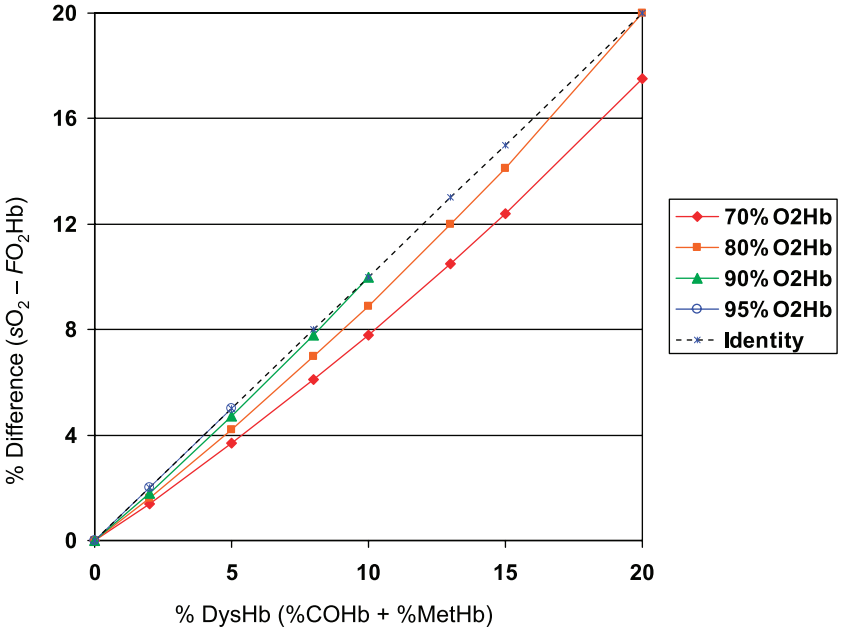

Figure 1. Plots of the % difference between sO_2 and FO_2Hb versus the % dyshemoglobins (%COHb + %metHb). sO_2 was calculated as % FO_2Hb/(100% − %dysHb).

but opposite to that of H^+ ion and pCO_2, their concentration should not be included in the definition of sO_2.

In an attempt to better distinguish between sO_2 and FO_2Hb, a new terminology was introduced by calling sO_2 "functional saturation" and FO_2Hb "fractional saturation." However, the addition of "functional" to "saturation" for designating sO_2 is redundant, and the term "fractional saturation" ignores the concept that "saturation" requires that the system can achieve full saturation, even in the presence of other ligands. The presence of COHb, for instance, does not prevent the remaining Hb from being fully saturated with O_2 (26). Thus, the concept of sO_2 applies to the remaining Hb and not to total Hb. A "saturation scale" by definition runs from 0 to 1, or 0 to 100% (26).

The similarity of these saturation terms actually contributes to the confusion. Moreover, their frequent use led to the fictitious concept of a "pulse oximeter gap" being the difference between these two different quantities (5). That different instruments supposedly measure different kinds of oxygen saturation suggests that the definition of sO_2 is method-dependent. The suggestion is reinforced by the use of the hybrid symbol Spo_2 for sO_2 as measured by a pulse oximeter. In cooximetry, multiwavelength spectrophotometry measures the concentration of the multiple Hb derivatives (27) from which several quantities can be calculated: ctHb, sO_2, FO_2Hb, FCOHb, FmetHb, BO_2, ctO_2 etc. When sO_2 values are reported by blood gas analyzers, cooximetry is in line with pulse oximetry. However, the substitution of FO_2Hb instead of sO_2 in the cooximetry method described by Brown (1) has led to the present widespread confusion of these terms.

Is the difference between sO_2 and FO_2Hb a concern in routine reporting of blood gas reports? For clinicians who understand the differences, either parameter could be used, especially if reported with the appropriate reference interval. Because the COHb and metHb are usually no more than about 2% of the Hb, the sO_2 and FO_2Hb typically differ by only a small amount. However, confusion arises when either (a) both parameters are used interchangeably, (b) inappropriate reference intervals are used, or (c) the concentration of dysHb becomes large. The ubiquity of pulse oximeters ensures the widespread use of sO_2, and so conformity with blood gas/cooximetry reports would be beneficial. In such reports, the sO_2 could replace the FO_2Hb when reported along with the COHb and metHb values, but we do not believe that both sO_2 and FO_2Hb should be reported together. We have observed cases where inappropriate reference intervals are used, such that the FO_2Hb was reported along with the reference range for sO_2. As shown in Figure 1, the % difference (sO_2 − FO_2Hb) increases approximately linearly as the %dysHb increases. Therefore, when either COHb or metHb levels are increased, the sO_2 and FO_2Hb become markedly different, which could more likely cause a misinterpretation of the FO_2Hb.

Being unaffected by the dysHbs, the sO_2 is physiologically more specific for monitoring pulmonary oxygenation than FO_2Hb. Thus, the sO_2 becomes a parameter that specifically monitors oxygen saturation, whereas the COHb and metHb specifically identify the amounts of dysHb present. The inadequacy of reporting either FO_2Hb or sO_2 without the COHb and metHb values was highlighted in a report of a patient with methemoglobinemia, who was introduced as "a woman with low oxygen saturation (28)." Only after working through a long differential diagnosis was the tentative conclusion reached that a dysHb might be present. If the dysHb fractions had been reported along with either the FO_2Hb or sO_2, the correct diagnosis would have been reached immediately.

Because CO increases the O_2-affinity of Hb, one could argue that a decrease in FO_2Hb coincides with a decreased O_2 availability to the tissues. However, clinicians must have sufficient understanding of O_2 physiology to differentiate whether this is caused by a decreased pO_2 and O_2 content, an increased O_2 affinity of Hb due to CO (29) or other factors, or both. Both COHb and metHb increase the O_2-affinity and shift the ODC to the left. This effect is quantitatively expressed by the relationship of standard-p_{50} and *F*dysHb, as given for COHb in Eq. 8 (14,29):

$$p_{50} = -3.6 * FCOHb + 3.4 \quad (8)$$

It follows from Eq. 8 that at $FCOHb = 0.35$, $p_{50} = 2.14$ kPa (16 mm Hg). Consequently, in the presence of COHb, pO_2 must decrease to a considerably lower level for the release of the amount of O_2 needed by the tissues. The diffusion of O_2 to the most unfavorably situated cells becomes even more difficult, with hypoxia more likely. MetHb has a similar effect, but to a lesser degree (14). Because dysHbs influence O_2 affinity as well as BO_2, they should be reported separately, in addition to sO_2.

Although FO_2Hb has a clear analytical definition, it lacks a clear physiological meaning and is a less specific parameter than sO_2. Because FO_2Hb depends on pO_2 as well as on the dysHb fractions, a low FO_2Hb may signal a decreased sO_2, or an increased dyshemoglobin fraction, or both. One study (30) clarified several misconceptions and emphasized the importance of including the dysHb fractions with the FO_2Hb, as would also be the case with sO_2. As mentioned earlier, listing two saturation measurements on the same report could cause even more confusion.

The problems described here can be solved by standardization of both the instrument readouts and the clinical reports, so that *c*tHb, sO_2, *F*COHb, and *F*metHb are displayed separately. This requires participation and cooperation of international organizations, such as the International Federation of Clinical Chemistry, and the companies that produce the instruments.

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The Light–Tissue Interaction of Pulse Oximetry

Paul D. Mannheimer, PhD

The underlying science of pulse oximetry is based on a simple manipulation of the Lambert–Beer law, which describes the attenuation of light traveling through a mixture of absorbers. Signals from detected red and infrared light that has traveled through blood-perfused tissues are used to estimate the underlying arterial hemoglobin oxygen saturation. However, light scatters in tissue and influences some of the simplifications made in determining this relationship. Under most clinical circumstances, the empirical process that manufacturers use to calibrate the system during its design readily accommodates this and results in accurate readings. The same tissue light scattering properties allow sensors to be configured for use on opposing or adjacent surfaces, provided that the placement sites offer sufficient signal strength and are absent factors known to influence accuracy. In this paper I review the light–tissue interaction in pulse oximetry and describe some of the assumptions made and their implications. Certain deviations from the nominal conditions, whether clinical in nature or misuse of the product, can affect system performance. Consequently, users should be cautious in modifying sensors and/or using them on tissue sites not intended by the manufacturer (off-label use). While perhaps helpful for obtaining pulsatile signals or extending the lifetime of a sensor, some practices can disrupt the optical integrity of the measurement and negatively impact the oxygen saturation reading accuracy.

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Clinical interest in monitoring oxygenation derives from the importance of the oxygen molecule to living organisms: without adequate delivery to the vital organs and tissues, metabolism cannot be supported and cells (and the organism) die. Pulse oximetry has been used for monitoring patient oxygenation during anesthesia since the mid 1980s and was quickly adopted as a standard of care for anesthesiology and critical care medicine (1,2). Its ability to provide early indications of hypoxemia, coupled with its ease-of-use, has popularized its adoption in many hospital and home settings. Many manufacturers provide multiple choices of monitoring configurations as well as reusable and single patient-use sensors to cover a broad range of patient populations and placement sites, all testament to the clinical and commercial success of the technology.

Pulse oximeters estimate the true hemoglobin oxygen saturation of arterial blood (Sao_2) by measuring the heart beat-induced changes in light transmission through a blood-perfused tissue. Oxyhemoglobin (O_2Hb) absorbs visible and infrared (IR) light differently than does deoxyhemoglobin (HHb) and appears bright red under white light illumination as opposed to the darker brown HHb. Isolating the color of the modulating signal component assesses the degree to which the arterial blood contains red O_2Hb or brown HHb; contributions from other tissue components that absorb and scatter light are generally unchanging during this time scale and (in concept) minimally affect the estimate.

The basic mathematics of pulse oximetry can be derived through an algebraic manipulation of the Lambert–Beer Law (3). This fundamental tenant of spectroscopy describes how light intensity decays as it passes through a nonscattering, light-absorbing substance comprised of one or more components. Aoyagi used this concept when he engineered the first modern-era pulse oximeter in the early 1970s (4). Even today, several decades later, all commercially available pulse oximeters follow this same basic relationship. While effective in forming the mathematical basis, this simple derivation of pulse oximetry misses an important factor: light scatters as it travels through living tissues, significantly impacting the assumptions made in the Classical Lambert–Beer Law description of pulse oximetry.

The following work reviews the light–tissue interaction in pulse oximetry and those factors accommodated by the system's empirical calibration. However, depending on the patient's clinical status and how and where the sensor is applied, reading accuracy can be meaningfully impacted when remaining assumptions

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inherent in the technology are compromised. Understanding these factors and using sensors properly will help to ensure pulse oximetry provides accurate and reliable information.

LIGHT TRANSMISSION AND THE MATHEMATICS OF PULSE OXIMETRY

The fractional transmission (T) of light through a series of N optical filters can be written as the product of the transmission through each of the individual filters, since each one attenuates the light that is incident upon it:

$$T_{\text{overall}} = I_{\text{out}}/\text{I}_{\text{in}} = T_1 \cdot T_2 \cdot T_3 \cdot \ \ldots \ \cdot T_N \quad (1)$$

where I_{in} and I_{out} are the incident and emerging light intensities, respectively. Unity transmission indicates that all of the incident light passes through the filter without loss, while zero transmission represents no light passing through. As suggested by Eq. 1, reordering or repartitioning the filters results in the same overall transmission. In pulse oximetry, conceptually, we can think of the transmission of the light traveling between the sensor's emitters and photodetector as a similar series of optical filters:

$$T_{\text{overall}} = \eta_{\text{LED-tissue}} \cdot T_{\text{pigment}} \cdot T_{\text{skin}} \cdot T_{\text{bone}} \cdot T_{\text{venous}} \cdot T_{\text{arterial}} \cdot \ \ldots \ \cdot \eta_{\text{tissue-detector}} \quad (2)$$

where the two eta (η) terms refer, respectively, to the coupling efficiency of light emitted by the sensor's light emitting diodes (LEDs) reaching the tissue and the efficiency with which the re-emerging light is collected by the photodetector. Each of the remaining terms refer to the light transmission through the skin's pigment (melanin), the skin itself, bone, veins, arteries, and other absorbers such as tendons, capillaries, etc.

Absorbance (A) describes how much light does not pass through (*absorbed*), and is defined as the negative logarithm of transmission. Rewriting Eq. 2 in terms of absorbance,

$$A_{\text{overall}} = -log(T_{\text{overall}}) = -log(\eta) - log(T_{\text{pigment}}) - log(T_{\text{skin}}) - log(T_{\text{bone}}) - log(T_{\text{venous}}) - log(T_{\text{arterial}}) - \ \ldots \quad (3)$$

Pulse oximetry focuses on the *change* in absorbance over the cardiac cycle. Consider each transmission term in Eq. 3 as being a function of time. Typically, only the arterial term changes over the time frame of a heart beat. Taking the time-derivative of Eq. 3 (or its difference at two points in time along the cardiac cycle) eliminates each of the terms except for T_{arterial}

$$d(A_{\text{overall}})/dt = -dlog/dt(T_{\text{arterial}}[t]) \quad (4)$$

The Lambert–Beer Law, dating back to the mid 1800's (5) [as cited by Severinghaus and Astrup (6)], quantifies light absorbance along a well-defined path length in terms of the characteristics and concentrations of the uniform mixture of individual components:

$$A \equiv -log(I_{\text{out}}/I_{\text{in}}) = l \cdot \sum_i (\beta_i \cdot cX_i) \quad (5)$$

where l is the path length through the medium, and β_i and cX_i are the spectral absorption characteristics and concentration of each of the i^{th} substances in the optical path. The basic formulation of pulse oximetry comes from combining Eqs. 4 and 5. Considering the two primary light absorbers in the blood to be O_2Hb and HHb, and measuring the ratio of cardiac-induced modulating light levels at two different wavelengths:

$$R = \frac{[dlog(I_{\text{out}})/dt]_{\lambda_1}}{[dlog(I_{\text{out}})/dt]_{\lambda_2}} \approx \frac{(AC/DC)_{\lambda_1}}{(AC/DC)_{\lambda_2}} \quad (6a)$$

$$= \frac{((S\beta_{\text{O2Hb}} + (1-S)\beta_{\text{HHb}}) \cdot \Delta cHb_{\text{a}} \cdot l)_{\lambda_1}}{((S\beta_{\text{O2Hb}} + (1-S)\beta_{\text{HHb}}) \cdot \Delta cHb_{\text{a}} \cdot l)_{\lambda_2}} \quad (6b)$$

where in Eq. 6a R is the Modulation Ratio, λ_1, λ_2 refer to two wavelengths of light, and AC and DC refer to the alternating and average (constant) portions of the detected photosignals, respectively (Fig. 1). In Eq. 6b, S is the true arterial hemoglobin oxygen saturation value ranging from 0 to 1, and ΔcHb_{a} is used here to indicate the change of the arterial hemoglobin concentration within the optically probed tissue bed over the time increment.[1] Most commonly, λ_1 and λ_2 are, respectively, near 660 nm (red light) and in the near IR

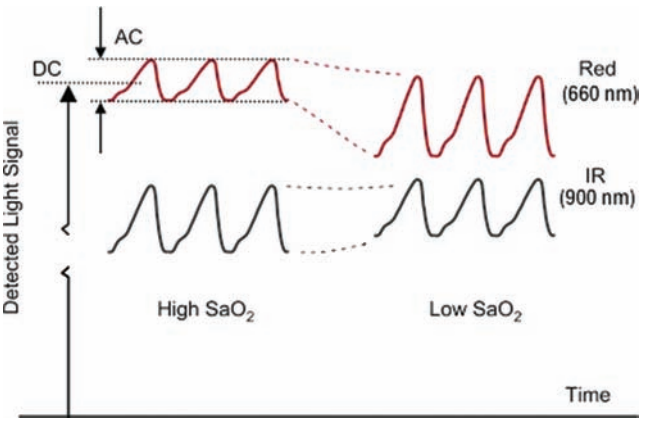

Figure 1. Red and infrared light signals are modulated by the cycling blood volume in perfused tissues. At high Sao_2, the red pulse amplitude (AC/DC, where "AC" is the alternating component and "DC" is the average component as indicated in the figure) is smaller than in the infrared, while the relative amplitudes are reversed at low saturation. Note the signal level waveform shape is inverted from a blood pressure waveform. The incremental increase in tissue blood concentration at systole results in less light reaching the photodetector than at diastole.

[1]Some descriptions of pulse oximetry consider the tissue blood concentration to be constant over the duration of the cardiac pulse and model alternatively a path length change due to the increased arterial blood content. The more precise description would be to consider the $l{\cdot}cHb_{\text{a}}$ product to change over the cycle.

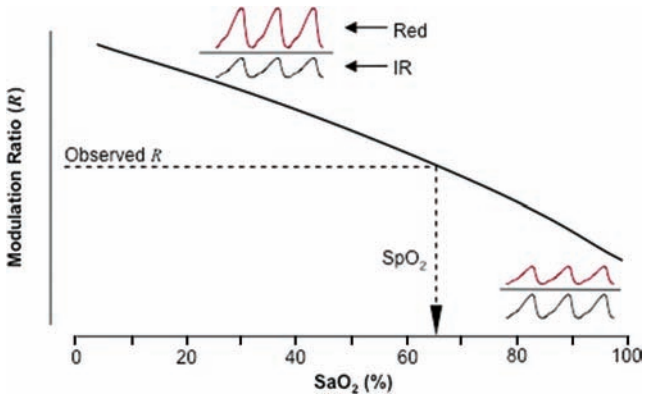

Figure 2. Red/Infrared Modulation Ratio (R) versus Sao_2. At high Sao_2 (right side of the graph), pulse amplitude (or modulation) of the red signal is less than that of the infrared signal, while the reverse is true at low Sao_2. Pulse oximeters measure R, the ratio of red to infrared pulse amplitudes (Eq. 6a), and estimate Sao_2 by applying the calibration curve (the solid line) as depicted by the dashed line and arrow. Modulation Ratio is also sometimes referred to as "Y" or "ϕ".

near 900 nm or 940 nm. At high oxygen saturations, with the arterial blood comprising predominantly O_2Hb, the detected red pulse amplitude (AC/DC) is approximately half the IR pulse amplitude. As the saturation decreases, with increasing amounts of HHb in the arterial blood, modulation of the red signal increases, while it shrinks slightly in the IR (Fig. 1). Solving Eq. 6b for the variable S results in an estimate of arterial oxygen saturation (Spo_2), derived from the measured value of R (Fig. 2).

THE INFLUENCE OF LIGHT SCATTERING

The simple Lambert–Beer Law derivation of pulse oximetry assumes a single, well-defined light path common to each of the wavelengths that pass through the tissue. This results in the wavelength-independent l and ΔcHb_a terms in Eq. 6b presumably cancelling one another. Visible and near IR light, however, are strongly scattered by human tissue; the detected light is more accurately described as an *ensemble* of independent photon paths (7,8). Some of the detected photons travel shorter routes without migrating far from the direct line between the emitter and detector, and some scatter farther from this line without being absorbed or lost at a boundary (photons that are absorbed or lost cannot contribute to the photocurrent). The longer-traveled photon routes provide more interaction with blood, and the incremental difference between systolic and diastolic concentrations of tissue blood creates a greater impact on the relative number of survivors (greater detected pulse amplitude). Conversely, detected photons traversing the shorter distances are less exposed to the cycling blood level and survive with a more uniform likelihood between systolic and diastolic conditions (smaller detected pulse amplitude). In general, as the absorption of the light increases, detected light tends to come from the

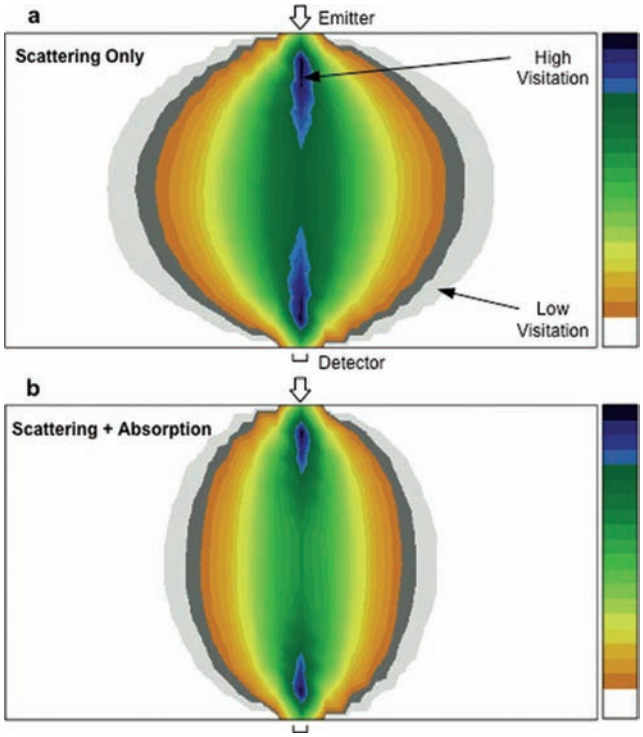

Figure 3. Relative visitation probabilities based on a Monte-Carlo random walk of photons are shown for red light transmitted through a simulated homogeneous tissue slab in (a) the absence of absorption and (b) with absorption consistent with human tissues. Slab dimensions are approximately 10 mm by 20 mm, with the point emitter positioned at the top and point detector at the bottom. Regions traveled most commonly by the migrating photons that reach the detector are shown as dark blue, progressing through green, tan, and gray, each indicating decreasing visitation. Photons that are absorbed or reach the top or bottom surface other than at the detector are considered to be lost (not detected); their routes accordingly do not contribute.

shorter paths (9). Figure 3 illustrates this graphically using the results of a random walk model for photons scattering through a slab [model construct similar to that described in (10)]. As the probability for a photon becoming absorbed at any given step increases (higher absorption), fewer surviving routes reach the periphery. Figure 4 provides the path length distributions according to Patterson et al. (7), considering the same scattering and absorption conditions. The final detected photosignal comprises a mixture of all surviving photon paths, and convolves pulse amplitudes coming from all of the various path lengths.

To account for these effects in the Lambert–Beer Law model and Eq. 6, l may be replaced with $\langle l \rangle$, a representation of the *effective mean path length* of the detected light, combining all of the effects of scattering into a single term (10). Making this replacement results in the Modified Lambert–Beer Law (11). Commercial pulse oximeter systems are empirically calibrated in studies conducted on healthy adult volunteers to correlate the measured values of R (per Eq. 6a) to sampled arterial blood Sao_2 values measured with a CO-oximeter

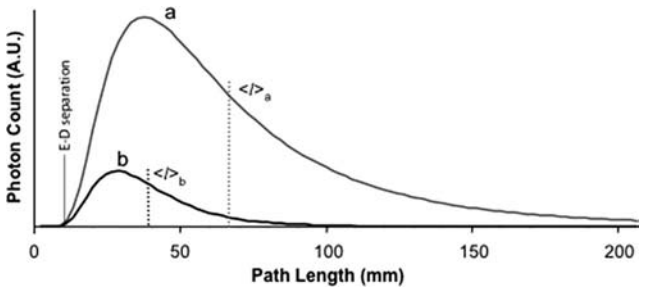

Figure 4. Path length distributions for detected photons are shown for the scattering-only (a) and scattering + absorption (b) conditions depicted in Figure 3. Each photon's path length is effectively a product of the number of steps taken in its random walk to the detector and their step size. Notice that as the absorption increases, not only are fewer total photons detected, but the distribution shifts toward the shorter routes. The vertical dotted line in each curve indicates their respective mean path lengths $\langle l \rangle$ values that are several times greater than the physical separation between the emitter and photodetector (E–D separation). The likelihood that a surviving photon travels the minimum distance directly across the slab without being scattered away from the straight line is exceedingly small; path lengths less than the E–D separation are impossible.

(12). This empirical process incorporates the actual average ratio of red and IR $\Delta cHb_a \cdot \langle l \rangle$-values observed in human tissues into the calibration.

REFLECTANCE VERSUS TRANSMISSION PULSE OXIMETRY

Is there a meaningful difference between reflectance and transmission pulse oximetry technology? From the perspective of light transmission through the tissue bed, the answer is no, provided the emitter-detector separations are comparable to each other and are on the order of many scattering-lengths or greater in magnitude (13). Once the photon has traveled a sufficient distance to have lost the history of its past (approximately 1 mm in tissue for pulse oximetry wavelengths), there is little, if any, difference where the detector is located. Indeed, *reflectance* and *transmission* are best thought of as convenient manufacturing terms for sensors that have emitters and detectors located on either the same or opposite sides of a tissue bed. (The term "reflectance" is an unfortunate descriptor for this type of sensor geometry, as it improperly implies a requirement for some form of subdermal mirror to reflect the light back to the detector. An alternative and more generic term is "surface sensor.") From an optical perspective, both geometries measure the *diffusion* of light through a blood-perfused tissue bed. Figure 5 illustrates this as the glow of the red scattered light re-emerging from the tissue. In both cases, at a distance of several millimeters from the emitter, substantial volumes of tissue have been visited by the exiting photons, independent of which specific adjacent or opposing location is selected. This is further illustrated by observing the pulse amplitude of the photoplethysmograph using transmission and surface (reflectance) sensor geometries (Fig. 6). Pulse amplitude measured on the finger was approximately 3% in this example, regardless of emitter–detector orientation, while the measurement on the forehead, using the same surface sensor on the same individual, yielded a pulse amplitude closer to 1%.

The relationship between the pulse oximeter's measured value of R and blood Sao_2 is very similar between transmission and reflectance geometry sensors, with the small difference readily accommodated by proper device calibration (unpublished data). Performance factors that are commonly attributed to the geometry of the sensor optics, such as weak signals or venous pulsation, are more appropriately related to the anatomy and physiology of the various sensor placement sites, and will be discussed further in a later section.

THE "PULSE" IN PULSE OXIMETRY

The difference in pulse amplitude between the forehead and finger noted above highlights an interesting and poorly understood aspect of pulse oximetry and photoplethysmography in general; where does the optical "pulse" actually come from? Pragmatically, this measure of signal strength (i.e., the magnitude of re-emerging light intensity variation that continuously cycles with the beating heart) comes directly from the modulating change in tissue opacity (optical density). Factors that have been noted to affect this include:

1. The periodic increase and decrease in the tissue blood fraction (14),
2. Spacing between the emitter and detector (wider separations associated with larger measured pulse amplitudes), and the depth of the pulsing vasculature (15), and
3. The extinction coefficient of the modulating blood volume at the measurement wavelength (16).

Additional proposed contributors to the optical pulse include

4. Volumetric and flow-dependent blood-scattering contributions from the erythrocytes in the blood (17),
5. Pulsing flow in venules supplied by arteriovenous anastomoses (18),
6. Venous pulsations, direct from the right heart or indirectly from adjacent arteries (19,20), and
7. The degree of cutaneous vessel distensibility (i.e., local vessel compliance as affected by sympathetic stimuli) (21), as this would affect the changing local tissue blood fraction.

Larger pulsing vessels can also contribute to the optical pulse, but have been associated with disruptions to accurate pulse oximetry (22,23), and are absent from the distal regions of the finger or toe where strong pulsatile signals are commonly observed.

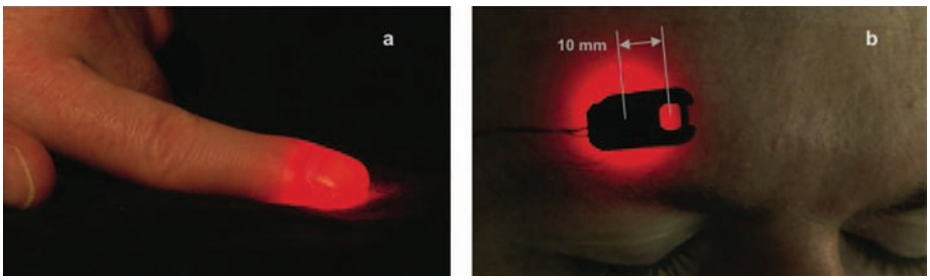

Figure 5. (a) When a finger is illuminated by a pulse oximetry sensor's emitter placed under the pad, the entire fingertip glows. It matters very little if the detector were to be positioned across the finger about 1 cm from the emitter, or about 1 cm away on the same side—similar amounts and types of tissue are being probed by the detected light. (b) Sensors using the reflectance geometry similarly detect light that diffuses through the perfused tissue bed. Shown here is the emitter of a disassembled forehead sensor placed against the skin (hidden by its opaque plastic carrier). The sensor's detector has been removed from the aperture to the right. Although the emitter and detector are positioned on the same side, the detected light penetrates well into the surrounding tissues.

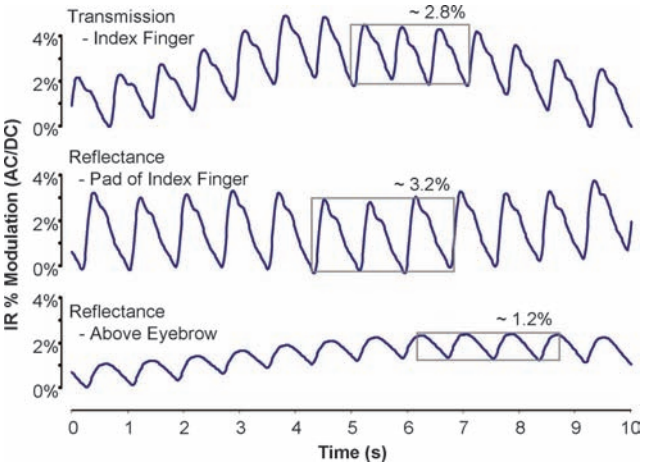

Figure 6. The photoplethysmographic pulse amplitude (infrared signal AC/DC) relates more to the anatomical site where the optics are placed than the sensor's emitter and detector orientation. These waveforms were acquired from the author's index finger using transmission (top) and reflectance (middle) geometries, while the bottom waveform comes from the forehead (acquired using the same reflectance sensor as with the middle waveform).

Empirically, pulse oximetry sensors placed on tissue regions with a rich presence of capillaries and arterioles (e.g., distal regions of the digits, the forehead, the earlobe, and nose) tend to demonstrate the strongest pulse amplitudes, at least in the absence of vasoconstriction that can affect most of these locations (24–26). Regions with very low vascular density, such as the skin of the torso, generally provide very weak optical pulse amplitudes. Indeed, taken in the extreme, a region devoid of vasculature would provide no change in light attenuation with the heart beat as it lacks blood flow altogether. While understanding the specific mechanism that creates the pulse remains an area of research, the optical pulse amplitude relates logically to the amount of distensible arterial vasculature that exists in the optically probed tissues.

TISSUE PERTURBATIONS AND PULSE OXIMETRY

Consider the ratio of the red and IR $\Delta cHb_a \cdot \langle l \rangle$ values found in Eq. 6b (making the substitution of l with $\langle l \rangle$). As noted before, the system's empirical calibration accommodates its nominal value for the sensors being used. Physio-optic changes in $\Delta cHb_a \cdot \langle l \rangle$, however, if not equivalent in the red and IR channels, will create a bias between Spo_2 and Sao_2, independent of any additional engineering hardware, software, or signal processing considerations. For example, a change or "perturbation" in tissue hemoglobin content compared to the normal healthy adults used for calibration can alter the value of $\langle l \rangle_{red}/\langle l \rangle_{IR}$ and create a bias in R and, consequently, Spo_2 readings. The ratio $\langle l \rangle_{red}/\langle l \rangle_{IR}$ inherently shrinks with Sao_2 ($\langle l \rangle$ decreases as light absorption increases) and is part of the calibration. With less than a normal amount of hemoglobin in the tissue, this ratio declines less with decreasing Sao_2 since the impact to $\langle l \rangle$ from increasing HHb content is greater in the red than IR part of the optical spectrum. This changes the R versus Sao_2 relationship in Figure 2, bending and rotating the curve clockwise about a point near 80% Sao_2 (13,27). Indeed, the tendency for Spo_2 to overestimate Sao_2 at high Sao_2, and more significantly, to underestimate it at low Sao_2, has been observed in anemic patients (28).

Vascular heterogeneity (different regional values of ΔcHb_a) can also impact Spo_2 if detected light paths at the multiple wavelengths differ significantly from one another. Similar to the decrease in $\langle l \rangle$ as absorption increases, the expanse of the detected light's migration also decreases (29). If overlap in these migration paths is poor, the red and IR light may be modulated differently by uneven distributions of pulsing vasculature, affecting the value of R and its correlation to Sao_2 (27). Additionally, migrating photons that encounter an opaque or strongly absorbing macroscopic object (such as a large blood vessel) will likely be removed from the ensemble before reaching the photodetector and consequently not contribute to the signal. Photon migration modeling suggests detected signals come predominantly from light that bypasses such objects and/or travels through regions with weaker absorption and scattering (30,31). (While attenuation is equivalent for light traveling through the middle of a 5-mm blood vessel as it is through a series

of ten 0.5-mm diameter vessels, with scattering, much of the detected signal strength comes from photons that have traveled through only a limited portion of the series. With the larger vessel, opportunity to avoid the absorber is absent.) The presence of such distinct static objects, or more importantly, one or more that change synchronously with the cardiac pulse, can greatly influence Spo_2 reading accuracy by disrupting the relationship between the measured value of R and the color of the underlying arterial blood (15,22,23). Numerous groups have developed physio-optic numerical models that explore such impact of homogeneous and nonhomogeneous tissue properties on pulse oximetry readings (10,13,15,17,32).

VENOUS PULSATION

One of the basic premises in pulse oximetry is that the change in optical density of the tissue due to the cardiac pulse comes only from arterial blood volume changes. Whether this is valid is unknown and relates back to discussions about the origins of the optical pulse. Nonetheless, the correlation of pulse oximeter Spo_2 values to invasively sampled arterial blood Sao_2 values is generally within a few percent. Several groups have observed situations in which tissue venous blood volume also appears to modulate synchronously with the cardiac cycle based on the appearance of the optical waveform morphology for sensors placed on the digits (19) or forehead (20). When both the arterial and venous blood "pulse" synchronously, pulse oximeter Spo_2 readings can reflect a mixture of the arterial and local venous oxygen saturation levels (33). Application of mild pressure to the sensor, however, has been found effective in reducing this artifact, as it appears to reduce or eliminate the pulsing venous volume in the optically probed regions of the tissue (20,34).

OPTICAL SHUNTING

When a sensor is applied poorly or lifted from the skin, in either transmission or surface geometries, some of the emitter's light may reach the detector while not passing through blood-perfused tissues ("shunted light"). Optical light shunts can exist external to the tissue (35,36), or in some conditions within the tissue itself if sufficient blood is forced out of the optically probed region (subdermal light shunt) (37). Optical shunting results in an artificial reduction of the plethysmograph pulse amplitude, independent of the underlying tissue blood volume changes or Sao_2 level since some of the detected light is never exposed to the pulsing arterial blood content. Unless the impact at the multiple wavelengths precisely cancels in the ratio taken in Eq. 6a, the Spo_2 reading will be affected. Whether the Spo_2 readings over- or underestimate the true Sao_2 depends on which of the red or IR signals (respectively) are more strongly shunted.

PHYSIO-OPTIC DO'S AND DON'TS

The presence of a resolvable pulse is a necessary but not sufficient condition for pulse oximetry.

While the basic principals of pulse oximetry may appear simple and elegant on the surface, the factors described above suggest there is more, literally, going on inside. Disruptions to the general optical environment present during a device's development can affect Spo_2 accuracy.

Patient conditions can at times challenge a pulse oximeter in acquiring a signal and some users may be compelled to *improvise* in order to obtain readings. Similarly, sensors are sometimes modified to extend the lifetime of otherwise "single patient-use" devices. Indeed, one can find numerous citations in the literature where authors describe off-label changes to the pulse oximeter sensor to target one or both of these goals (38–42). While it is not the intent of this discussion to categorically discredit such efforts, users should question whether these changes have maintained the optical integrity of the sensor and tissue site. Importantly, has the modified use been verified to provide proper Spo_2 readings over the full or clinically relevant Sao_2 range? Errors in readings tend to increase as the patient's Sao_2 decreases to $<90\%$ (13,15,23,27); spot-checking the agreement between Spo_2 and Sao_2 at normal high saturation levels does not, unfortunately, assure accuracy as the Sao_2 decreases. Regulatory and international standards require manufacturers to demonstrate, when used as labeled in controlled settings, Spo_2 reading accuracy meets its specified performance with data obtained and pooled over the full 70%–100% Sao_2 span (12,43). This is intended to ensure safety and consistency among commercially available systems; no such direct validation requirement is imposed on users who may chose to use these products differently. It would be impractical to require manufacturers to test the myriad of creative ways products can be misused.

Modifications generally fall into two categories, each with its own set of potential disruptions to the assumptions of pulse oximetry:

(A) Placement of sensors on alternate locations: Some tissue sites are simply incompatible with reliable and accurate pulse oximetry. The risk is that any of at least three optical factors described earlier can affect readings: 1) optical shunting (externally or within the tissue); 2) unexpectedly low or high tissue blood volume; or 3) pulses created by larger pulsing vessels. As monitors become more sensitive to weak signal levels, improperly placed sensors may appear to provide an adequate pulse waveform yet suffer from a physio-optic disruption.

(B) Modifications to sensors: The optical design of a sensor intended for specific applications may not be compatible with others. Adapting

a sensor by changing its housing or attachment method can further affect accuracy. This is particularly true if such modifications impact 1) optical shunting (externally or within the tissue), 2) the detected light's path length, or 3) the path length ratio.

For example, when peripheral pulse amplitudes become too small to acquire or maintain a signal, it is not an uncommon practice for users to try to find better pulsatile signals by adhering and/or clipping sensors designed for use on a patient's digit to an ear or across the forehead. While the resulting plethysmographic waveform, pulse rate and Spo_2 values may appear normal, the presence of a true hypoxia may be missed (44). We have also reproduced this scenario in the laboratory (adhesive digit sensor placed across the forehead or wrapped around the ear) and found Spo_2 readings to commonly overestimate the true Sao_2, at times posting 100% Spo_2 even when subjects are truly in the lower 70% range (unpublished data). Optically, these misapplied sensors are likely being affected by larger pulsing blood vessels and/or optical shunting (light traveling along the surface disproportionately shrinking the size of the red pulse amplitude).

To maintain accurate readings with pulse oximetry, as well as to ensure safety to the patient, sensors should only be used according to their labeled directions. Digit sensors, unless designed for use on other anatomical sites, should only be used on the digits. Reflectance and "Y-shaped" sensors should only be placed on the appropriate site(s) as directed in the labeling and not used elsewhere, even though these sensors' geometries may appear to be compatible with other locations. The proper device calibration and compatibility may not extend to alternative locations. Additional wraps, adhesives, or elastic bands are not recommended unless the product requires their use or specifically offers them as an option.

SUMMARY

Pulse oximetry is based on a relatively straightforward application of the Lambert–Beer law, using the change in signals corresponding to the cardiac cycle to isolate and estimate the patient's Sao_2. Light scattering, however, influences some of the simplifications made which, under most clinical circumstances, can be accommodated through the empirical process manufacturers use to calibrate the system during its design. Since red and IR light diffuses through the tissue, pulse oximetry sensors can be configured for use on opposing or adjacent surfaces, provided placement sites offer sufficient signal strength and are absent factors known to influence accuracy. However, certain optical perturbations can violate the remaining assumptions and impact system performance. Tissue heterogeneity, significant changes in tissue blood volume, venous pulsations, or shunting of light can all meaningfully influence Spo_2 readings, particularly at lower Sao_2 levels, if not adequately mitigated in the product's design or actual use. Users should be cautious in modifying sensors and/or using them on tissue sites not intended by the manufacturer (off-label use). Such practices may disrupt the optical integrity of the measurement and result in falsely reassuring Spo_2 readings.

To recap a summary of these principals: *The presence of a resolvable pulse is a necessary but not sufficient condition for pulse oximetry*. Accurate and reliable readings require that the integrity of the optical signals be maintained so that the Modified Lambert–Beer law assumptions remain valid.

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Dark Skin Decreases the Accuracy of Pulse Oximeters at Low Oxygen Saturation: The Effects of Oximeter Probe Type and Gender

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INTRODUCTION: Pulse oximetry may overestimate arterial oxyhemoglobin saturation (Sao_2) at low Sao_2 levels in individuals with darkly pigmented skin, but other factors, such as gender and oximeter probe type, remain less studied.

METHODS: We studied the relationship between skin pigment and oximeter accuracy in 36 subjects (19 males, 17 females) of a range of skin tones. Clip-on type sensors and adhesive/disposable finger probes for the Masimo Radical, Nellcor N-595, and Nonin 9700 were studied. Semisupine subjects breathed air-nitrogen-CO_2 mixtures via a mouthpiece to rapidly achieve 2- to 3-min stable plateaus of Sao_2. Comparisons of Sao_2 measured by pulse oximetry (Spo_2) with Sao_2 (by Radiometer OSM-3) were used in a multivariate model to assess the source of errors.

RESULTS: The mean bias ($Spo_2 - Sao_2$) for the 70%–80% saturation range was 2.61% for the Masimo Radical with clip-on sensor, −1.58% for the Radical with disposable sensor, 2.59% for the Nellcor clip, 3.6% for the Nellcor disposable, −0.60% for the Nonin clip, and 2.43% for the Nonin disposable. Dark skin increased bias at low Sao_2; greater bias was seen with adhesive/disposable sensors than with the clip-on types. Up to 10% differences in saturation estimates were found among different instruments in dark-skinned subjects at low Sao_2.

CONCLUSIONS: Multivariate analysis indicated that Sao_2 level, sensor type, skin color, and gender were predictive of errors in Spo_2 estimates at low Sao_2 levels. The data suggest that clinically important bias should be considered when monitoring patients with saturations below 80%, especially those with darkly pigmented skin; but further study is needed to confirm these observations in the relevant populations.

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Pulse oximetry estimates arterial hemoglobin oxygen saturation (Sao_2) from the ratio of the pulsatile to the total transmitted red light divided by the same ratio for infrared light transilluminating a finger, ear, or other tissue. The Sao_2 estimated by pulse oximetry (Spo_2) should therefore be independent of skin pigmentation and many other variables, such as hemoglobin concentration, nail polish, dirt, and jaundice. Several large controlled studies, including one comparing 380 African American and Caucasian subjects reported no significant pigment-related errors in pulse oximeter measurements at normal Sao_2 (1,2).

We recently examined the performance of three pulse oximeters (Nonin Onyx, Nellcor N-595, and Novametrix 513) and found a positive bias in Spo_2 in darkly pigmented subjects as large as 7% in the Sao_2 range of 70%–79% (3). That study, because of its relatively small size (21 subjects) and study design (subjects with either very light or very darkly pigmented skin, no intermediates), did not have the power to determine the relationship between differences in skin pigment, whether gender affected errors, and if oximeter probe type (e.g., clip-on versus adhesive/disposable) contributed to the errors.

A significant issue for pulse oximeter accuracy is finger size and geometry. In 20 yr of testing pulse oximeters, it is our impression that women, especially those with smaller fingers, tend to exhibit greater bias and variability in oximeter performance, especially at low Sao_2, although this has not been systematically examined.

On the basis of the above considerations, we designed this study to 1) determine the effect of a range of human skin pigmentation on pulse oximeter accuracy at a range of Sao_2 from 70% to 100%; 2)

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No manufacturers were involved in the selection of subjects, design, or conduct of experiments, data analysis, or manuscript preparation.

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Table 1. Demographics

Age	29 ± 5 (19–44)
Gender (M/F)	19/17
Ethnicity	
African American	17
Caucasian	12
Hispanic	3
Indian	1
Filipino	2
Vietnamese	1

determine whether gender affects pulse oximeter accuracy; and 3) determine whether probe type (adhesive disposable versus clip-on) affects the accuracy of Sao_2 estimates/Spo_2 values.

METHODS

The University of California at San Francisco Committee on Human Research approved the study, and informed consent was obtained from all subjects. Thirty-six healthy, nonsmoking subjects were studied. None of the subjects had lung disease, obesity, or cardiovascular problems. They ranged in age between 19 and 44 yr. We specifically sought subjects with a range of skin pigment for this study. Each subject's skin was categorized as light (Caucasian), dark (African American), or intermediate (others, Table 1), and confirmed in subject photographs by an observer blinded to saturation data/oximeter performance.

Subjects were studied while reclining in a semisupine position (approximately 30° head up) and deliberately hyperventilating air-nitrogen-CO_2 mixtures via a mouthpiece from a partial rebreathing circuit with 10- to 20-L/min fresh gas inflow. CO_2 was added to the breathing circuit to maintain end-tidal Pco_2 in low normal range. A nose clip prevented breathing of room air. A 22-gauge radial artery catheter was placed to facilitate arterial blood sampling for measurements of Sao_2. Six oximeters were mounted on each subject's fingers: a Nellcor N-595 with the OxiMax A disposable adhesive finger probe (Nellcor Inc., Pleasanton, CA), a clip-type Nellcor finger probe, a Masimo Radical (Masimo Inc., Irvine, CA) clip type and a Masimo Radical adhesive disposable type probe, and a Nonin (Nonin Inc., Plymouth, MN) 9700 clip type and a Nonin 9700 disposable adhesive probe. Spo_2 from the analog output connectors of the oximeters and the end-tidal gas values were recorded by a computer running LabVIEW 7.1 (National Instruments, Austin, TX). Oximeter probes were not mounted on the thumbs or little fingers.

A series of 11 stable target Sao_2 plateaus between 60% and 100% were achieved by an operator who adjusted the inspired air-nitrogen-CO_2 mixture breath by breath in response to the estimated Sao_2 derived from an oxyhemoglobin dissociation curve determined for each individual subject from mass spectrometer end-tidal gas analysis. Input parameters for the computer oxygen dissociation curve included arterial pH estimated from end-tidal partial pressure of CO_2, base excess adjusted if needed after each arterial blood sample was analyzed, and alveolar-arterial oxygen difference as needed, especially at low Sao_2, to attempt to match the predicted with the measured Sao_2. At each level, arterial blood was sampled after a plateau of 30–60 s had been achieved, followed by a second sample at the same plateau 30 s later. To promote good finger blood flow, each hand was wrapped in a warming pad. Five-second averages of Spo_2 values were taken at the end of the stable plateau and 30 s earlier, corresponding to the two arterial blood samples. Spo_2 values were eliminated for obvious signal dropout, or failure to reach an appropriate stable plateau. Functional Sao_2 (HbO_2/[hemoglobin + HbO_2]) was determined by multiwavelength oximetry (Radiometer OSM-3, Copenhagen, Denmark). Fractional Sao_2 was calculated from the functional Sao_2 and the measured levels of carboxyhemoglobin and methemoglobin. Quality control standards were run each day.

Bias was computed as Spo_2 minus Sao_2 from the reading of each oximeter and the corresponding blood sample value and is reported as mean ± SD. The relationship of bias to Sao_2 was analyzed by linear regression. Bias was also analyzed within decadal subgroups of Sao_2 (60%–70%, 70%–80%, 80%–90%, and 90%–100%). The effect of skin pigment group (dark, light, and intermediate), Sao_2 range or gender on bias was determined by Kruskal–Wallis or Wilcoxon's signed rank test, since variances were unequal. Multiple comparisons within skin pigment groups were made by the Tukey–Kramer HSD technique. Root mean square (RMS) error (square root of the sum of $[Spo_2 - Sao_2]^2$ divided by number of samples) was calculated as a measure of error magnitude. To analyze the effect of gender and skin pigment, RMS error was calculated for individual subjects within decadal Sao_2 ranges. The effect of skin pigment, Sao_2 interval and gender on RMS error was determined by Kruskal–Wallis or Wilcoxon's signed rank test. Multivariate (mixed-effects) models were used to analyze the effect of skin pigment, gender, age, hemoglobin, oximeter and probe combination, and Sao_2 on bias and RMS error. $P < 0.05$ was considered statistically significant. Statistical analysis was performed with JMP 5.1 (SAS Institute, Cary, NC).

RESULTS

Demographics

Seventeen female and 19 male subjects participated. Seventeen subjects were dark, 7 intermediate, and 12 light skinned. No differences in the distribution of male and female subjects were found in the different skin pigment categories. Subjects averaged 29 ± 5 yr (19–44 yr) (Table 1). Dark-skinned subjects were slightly older ($P < 0.01$), but there was no age difference between light- and intermediate-skinned subjects.

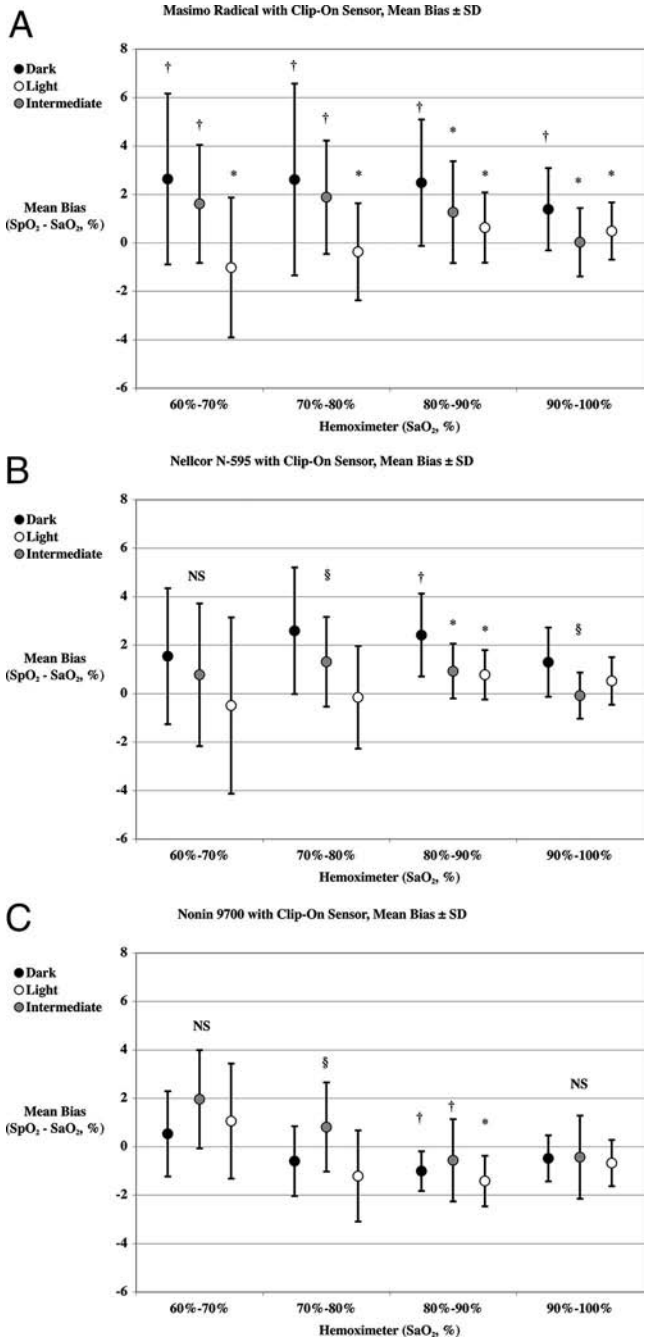

Figure 1. Bias (mean ± SD) for the three oximeters with clip-on finger probes in decadal ranges of oxyhemoglobin saturation. Bias is calculated as Spo_2 (oximeter-measured value of oxyhemoglobin saturation) minus Sao_2 (oxyhemoglobin saturation measured by a Radiometer OSM-3 multiwavelength oximeter). Light-skinned subjects are indicated by *open circles*, dark-skinned subjects by *closed circles*, and intermediate skin pigments with *gray circles*. Oximeter are: A. Masimo Radical, B. Nellcor N-595, and C. Nonin 9700. Statistical differences are indicated: *different from †; or §, all values statistically different from each other.

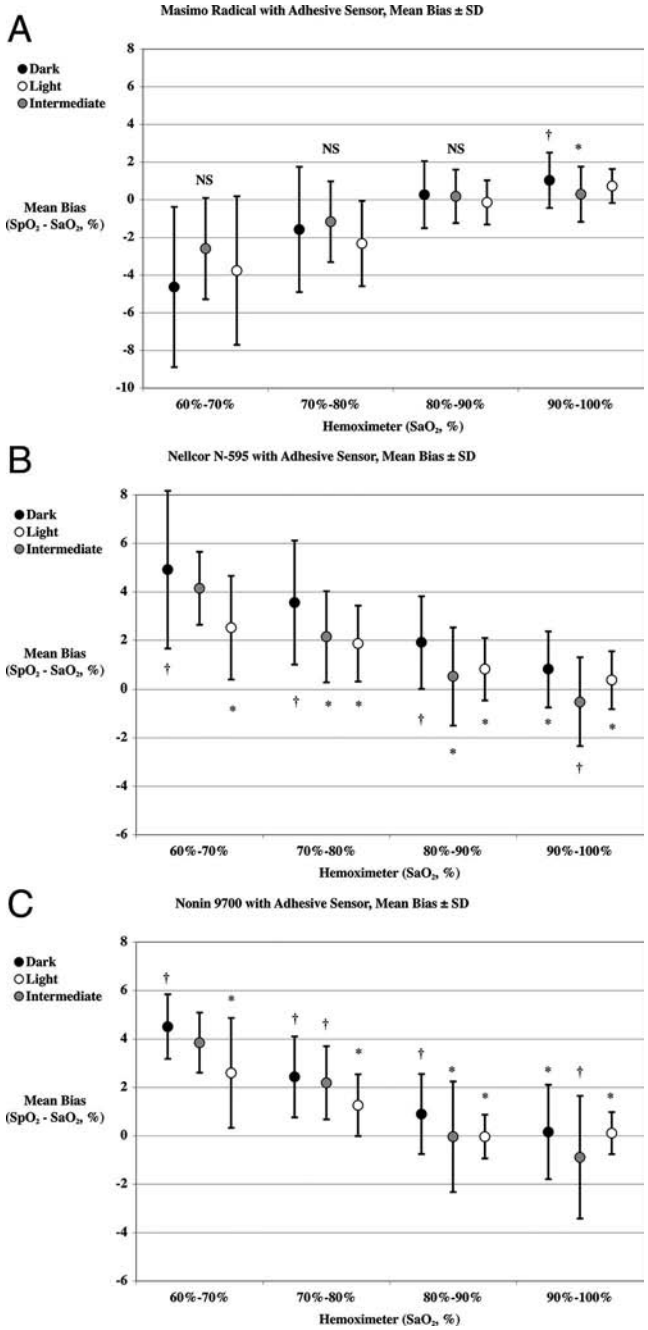

Figure 2. Bias (mean ± SD) for three oximeters with adhesive/disposable finger probes. Bias is calculated as Spo_2 (oximeter-measured value of oxyhemoglobin saturation) minus Sao_2 (oxyhemoglobin saturation measured by a Radiometer OSM-3 multiwavelength oximeter). Light-skinned subjects are indicated by *open circles*, dark-skinned subjects by *closed circles*, and intermediate skin pigments with *gray circles*. Oximeters are as follows: A. Masimo Radical, B. Nellcor N-595, and C. Nonin 9700. Statistical differences are indicated: *different from †; or §, all values statistically different from each other.

Bias

With the exception of the Masimo Radical with the adhesive finger probe, all instruments and probe combinations showed positive bias in intermediate- and dark-skinned subjects at low Sao_2 (60%–70% and 70%–80% saturation decades, Figs. 1 and 2). The greatest degree of bias was found with the adhesive probes; the Nellcor and Nonin adhesive probes showed bias of 4.5%–4.9% at 60%–70% saturation and 2.4%–3.6% bias at 70%–80% saturation with dark-skinned subjects. At the extreme, the Nellcor adhesive and the Masimo with clip-on probe read on average

Table 2. *P* Values for Multivariate Analysis of Bias ($Spo_2 - Sao_2$)

Oximeter	Gender	Skin pigment	Sao_2	Skin × Sao_2	Gender × Sao_2
Masimo Radical Clip-On	0.3	0.02	<0.0001	<0.0001	<0.0001
Nellcor N-595 Clip-On	0.8	0.0009	0.0005	<0.0001	<0.0001
Nonin 9700 Clip-On	0.4	0.06	<0.0001	<0.0001	<0.0001
Masimo Radical Adhesive	0.4	0.7	<0.0001	0.0007	<0.0001
Nellcor N-595 Adhesive	0.001	0.05	<0.0001	<0.0001	0.02
Nonin 9700 Adhesive	0.4	0.2	<0.0001	<0.0001	<0.0001

Sao_2 represents decadal range: 70%–80%, 80%–90%, and 90%–100%.

Table 3. *P* Values for Multivariate Analysis of Root Mean Square Error

Oximeter	Gender	Skin pigment	Sao_2	Skin × Sao_2	Gender × Sao_2
Masimo Radical Clip-On	0.09	0.01	<0.0001	0.01	0.8
Nellcor N-595 Clip-On	0.13	0.001	<0.001	0.049	0.9
Nonin 9700 Clip-On	0.03	0.07	0.02	0.7	0.003
Masimo Radical Adhesive	0.004	0.2	<0.0001	0.4	0.2
Nellcor N-595 Adhesive	0.01	0.049	<0.0001	0.3	0.3
Nonin 9700 Adhesive	0.7	0.02	<0.0001	0.3	0.051

Sao_2 represents decadal range: 70%–80%, 80%–90%, and 90%–100%.

nearly 10 points differently in dark-skinned subjects at 60%–70% saturation and seven points at 70%–80% saturation.

Pulse oximeter bias was significantly influenced by Sao_2 range for all oximeters and probe combinations (Figs. 1 and 2). The relationship between bias and Sao_2 was found to be similar statistically, whether analyzed by decadal Sao_2 range (Figs. 1 and 2) or by linear regression analysis (not shown). The pattern of bias varied according to oximeter configurations, with all except the Masimo Radical and adhesive probe showing increasing positive bias at low Sao_2. The analysis revealed essentially the same results when performed for fractional Sao_2 in place of functional Sao_2 (not shown).

Gender is a statistically significant determinant of pulse oximeter bias, with the magnitude of the gender bias differences varying with oximeter/probe type and Sao_2 range. With five of the six oximeter/probe combinations, females had greater bias in saturation estimates over the saturation range from 60% to 100%.

Multivariate Analysis: Effects of Skin Pigment, Gender, and Sao_2 on Bias

Multivariate analysis was used to examine relationships between skin pigmentation classification, gender, age, hemoglobin, Sao_2 and probe/oximeter combination and the outcome variable bias. The *P* values for these analyses are presented in Table 2 for each oximeter/probe combination separately.

Sao_2 was a highly statistically significant predictor of bias in all analyses. Although the results in Table 2 are shown for modeling Sao_2 as a continuous variable, the results were essentially the same when the analysis was performed with decadal ranges of Sao_2.

The effect of skin pigment on bias is also presented in Table 2. Skin pigment significantly predicted bias for the oximeters listed. Similar conclusions were reached when performing the analysis by the ethnicities shown in Table 1. However, the most robust statistical model included gender, skin pigment, and Sao_2, with the interaction terms of skin pigment with Sao_2 (Skin × Sao_2) and gender with Sao_2 (Gender × Sao_2) included. The interaction for gender with skin pigment was not statistically significant. Age was not statistically significant.

Hemoglobin and gender were too significantly correlated to be separated in the multivariate analysis, 11.8 ± 1.2 (women) vs 13.9 ± 0.8 (men), $P < 0.0001$. Hemoglobin was statistically significant in place of gender, but with both variables in the model, neither was clearly better.

RMS Error

Sao_2 range was a highly significant determinant of RMS error for all the groups shown in the tables except for male subjects using the Nonin 9700 and a permanent probe. Univariate analysis of the effect of skin pigment showed that dark-skinned subjects tended to have higher RMS errors, although this was not statistically significant within every Sao_2 range. RMS error for dark-skinned subjects was more than 3.0% in several of the gender/Sao_2 combinations.

Multivariate Analysis: Effects of Skin Pigment, Gender, and Sao_2 on RMS Error

Table 3 shows the results of multivariate analysis of how RMS error is influenced by gender, skin pigment, and Sao_2. Sao_2 range was a consistent predictor of RMS error, with error increasing at low Sao_2. Skin pigment and gender, or both, were also statistically significant factors with various oximeter–probe combinations. The interaction term for skin pigment with Sao_2 and gender with Sao_2 were also significant for some oximeter/probe combinations. Two oximeters, the Nonin 9700 with clip-on probe and the Masimo radical with the adhesive probe, did not show an effect of skin pigment, although both had a significant

gender effect. Age was not a statistically significant factor on RMS error magnitude.

DISCUSSION

Confirming a previous study (3), but expanding the oximeters and probes studied, we found that pulse oximeters generally overestimate Sao_2 in hypoxic subjects (Sao_2 values below 80%.) This bias was generally the greatest in dark-skinned subjects, intermediate for intermediate skin tones, and least for lightly pigmented individuals, although Spo_2 was underestimated by one type of oximeter, the Masimo Radical with the adhesive/disposable probe.

Theoretically, the ratio of the pulsatile to the total transmitted red light divided by the same ratio for infrared light should be dependent only on arterial saturation, making pulse oximetry independent of skin color. In practice, venous and tissue pulsation by mechanical force from nearby arteries causes deviations from this ideal. The chromatic characteristics of skin color arise from the interactions of light (primarily absorption and scattering) with the epidermis and the dermis. Because deoxyhemoglobin and melanin are the primary light absorbers in skin at the wavelength used for hemoglobin absorbance, the effective light-path for red light through the finger will vary with skin pigmentation. The magnitude of this effect will vary with skin pigment, tissue perfusion, and with finger geometry, and apparently with oximeter design. Therefore, pulse oximeter performance must be partly based on empirically determined correction factors obtained by *in vivo* comparison of oximeter readings with measured Sao_2 from arterial blood samples of volunteer subjects.

In our 20 yr of testing pulse oximeter accuracy, and probably in other testing laboratories, the majority of subjects have been light skinned. Most pulse oximeters have probably been calibrated using light-skinned individuals, with the assumption that skin pigment does not matter. In addition, several studies have shown that skin pigment does not produce errors in Spo_2 estimates at high Sao_2 ranges (1,2). The current data show that skin pigment introduces a positive bias at low Sao_2 in the Nonin, Masimo, and Nellcor instruments. Our previous study (3) reported similar findings for the Nellcor N-595 clip-on sensors, and for Nonin Onyx and Novametrix 513.

An important finding in the current study is that there is probably a continuous quantitative relationship between skin pigment and oximeter bias. This is seen in Figures 1 and 2 in which, for every oximeter and probe combination, light skin produced the smallest bias across the Sao_2 range, intermediate skin tones an intermediate degree of bias, and dark skin the greatest bias. Our earlier study (3) maximized power by studying only two extremes of skin pigment: very dark and very light. The current study enrolled subjects with a full range of skin pigment. The fact that the Spo_2 bias changes in an ordered relationship with skin pigment strongly indicates that our findings are due to skin pigment itself, rather than from some other effect. To further pursue this question, we performed all the univariate and multivariate analyses of bias with skin color quantified with a numerical scale (Munsell number) measured by a commercial color laboratory from photographs of the subjects' hands. This analysis, done by treating skin Munsell number as continuous variable, was not significantly more robust statistically than the simpler categorization of dark, light, and intermediate skin pigment groups, and we have omitted the data here.

As clearly seen in Tables 2 and 3 and Figures 1 and 2, Sao_2 is a highly significant determinant of pulse oximeter bias. The most common pattern with early model oximeters was negative bias at lower Sao_2 levels. Newer oximeters exhibit both positive and negative bias patterns for different oximeter/probes combinations. Because of the fundamental influence of Sao_2 on bias, it is essential to account for this effect when analyzing additional influences such as skin pigment and gender. Therefore, all data are presented in the context of Sao_2 range, and analyzed with respect to Sao_2 range or continuous Sao_2 value.

Gender was a statistically significant univariate predictor of pulse oximeter bias. This observation may relate to smaller finger size and a correspondingly smaller pulsatile signal detected by the sensor, a variant of the problem with light attenuation due to dark skin pigmentation. The female subjects had lower levels of hemoglobin, which was statistically significant in place of gender. Because lower hemoglobin was so highly associated with female gender, it was not possible to statistically separate the contributions of gender and low hemoglobin to oximeter error or bias. Anemia was previously reported to increase bias in pulse oximetry (4). We also cannot eliminate the influence of other confounding variables that we did not measure.

The univariate analyses presented in the tables and figures have important limitations. For example, the possibility of confounding influence among skin pigment, gender, Sao_2, and age might affect the results. Further, we recognize that while specific combinations of gender, skin pigment, and Sao_2 values produce statistically significant differences, the overall statistical significance of the variables themselves is of greater relevance. Multivariate analysis (Table 2) confirmed this highly significant influence of Sao_2 on bias. The most robust statistical model included the interaction of Sao_2 with both gender and skin pigment. Also, interaction terms were more important than the influence of both variables themselves. This interaction is clearly seen in the data: bias is not greatly affected by gender or skin pigment at higher Sao_2, but increases with oxyhemoglobin desaturation. Age was not a statistically significant variable in the multivariate analysis, although the age range of our

healthy subjects was smaller than might be encountered clinically.

This study and a previous study (3) have found that five types of oximeters show varying degrees of bias at low Sao_2, suggesting that this bias is a general feature of oximeter design. However, the clip-on probes generally exhibit less bias than the adhesive probes, suggesting that design of sensors or software can affect oximeter accuracy. Because we tested only three types of oximeters in this study and three in a previous study (3), our results may not apply to pulse oximeters made by other manufacturers.

Variability, as measured by RMS error, also increased because of skin pigment. Unlike bias, where positive and negative values may average to give a low mean value, RMS error will also be high with higher variability of bias. RMS error increases at lower Sao_2, which was the most important variable. Gender was a small, but statistically significant, factor for several oximeter–probe combinations. Skin pigment was not a statistically significant variable for two oximeters: the Nonin 9700 with clip-on probe and the Masimo radical with adhesive probe. However, similar to the effect of skin pigment on bias, the RMS error was higher in darkly pigmented individuals. RMS error for Sao_2 of 70%–100% is used for Food and Drug Administration device approval. Above 3.0 is not acceptable, yet there were several instances of oximeter–probe combinations with values over 3.0. Nearly all values over 3.0 are seen for darkly pigments subjects, and none for lightly pigmented.

The magnitude of the pulse oximeter error due to dark skin pigmentation is relatively small at Sao_2 values more than 80%, and probably of no general clinical significance. However, in individuals with darkly pigmented skin, bias of up to 8% was observed at lower Sao_2 levels, which may be quite significant under some circumstances. For example, in congenital heart disease, many patients have stable low Sao_2 values, and accuracy in an outpatient setting or during surgery may be desired. At high altitude, pulse oximeters are frequently relied on for accurate readings in both research and clinical settings, and the bias at lower Sao_2 may be important. Furthermore, studies examining ethnic differences in treatment responses based on Sao_2 as determined by pulse oximetry (e.g., treatment of lung diseases) need to account for differences in oximeter readings between light and darkly pigmented subjects. This may be relevant for the United States Food and Drug Administration or to other regulatory bodies to consider this in designing pulse oximeter accuracy standards.

We conclude that skin pigmentation, gender, and type of oximeter probe all affect pulse oximeter bias and error at low Sao_2 with a bias of approximately +5% at 75% saturation seen in three manufacturers' instruments. These deviations may be clinically relevant in some situations.

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Hemoximetry as the "Gold Standard"? Error Assessment Based on Differences Among Identical Blood Gas Analyzer Devices of Five Manufacturers

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BACKGROUND: The calibration and testing procedures of a pulse oximeter with arterial blood samples from healthy subjects are based on reference values from the hemoximeter. There are no tests to identify the accuracy of the reference devices. Because of this limitation and since the true values of oxygen saturation (sO_2 in %) in blood samples were not known, we used the differences between two identical devices, A and B, for error assessment.

METHODS: Two identical devices, A and B, from five leading manufacturers were investigated. Seventy-two arterial blood samples from 12 healthy volunteers at three different levels of saturation between 100% and 70% sO_2 were randomly evaluated by the test systems.

RESULTS: The observed differences (Δ) between Devices A and B, as a measure for the error of the hemoximeters, increased significantly with all manufacturers from level 97 (Δmin, −0.9%; Δmax, 2.6%) to 85 (Δmin, −2.4%; Δmax, 4.3), this effect was even stronger between levels 97 and 75 (Δmin, −4.6%; Δmax, 4.3%). A variance proportion analysis revealed the concentration of the reduced hemoglobin as the main error source for sO_2 measurements. Independent from the sO_2 levels there were also significant differences for the carboxy hemoglobin concentration in the range of 0%–4% and for the methemoglobin concentration in the range of 0%–1%.

CONCLUSIONS: The variance of sO_2 measurements between identical devices increased significantly when saturation decreased from the normal level of 97% to the hypoxemic levels of 85% and 75%.

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There is no test system for identifying the measurement error of the reference procedure for pulse oximetry, i.e., hemoximetry, also known as CO-oximetry. Hemoximetry discontinuously measures hemoglobin oxygen saturation and dyshemoglobines from blood samples. All medical devices deliver the measured values with a certain error.

CO-oximetry or hemoximetry is an essential component of blood gas analyzer systems. Hemoximetry presents hemoglobin oxygen saturation, dyshemoglobines, and total hemoglobin concentration data. The functional oxygen saturation measured by this procedure is the basis for calibrating pulse oximeters. Pulse oximeters cannot be calibrated using physical procedures, but only by directly comparing the reported measurements and the parallel arterial oxygen saturation measured by hemoximetry in a group of healthy subjects (1). Thus, the errors of hemoximetry are carried over into measurements made by the pulse oximeter.

There is no standard procedure for checking the measurement error of the hemoximeter. Usually the devices are calibrated by the manufacturer before delivery. For calibrating hemoximetry in everyday clinical routine, aqueous solutions supplied by the manufacturers are used. A gravimetric procedure that cannot be applied in normal clinical routine has been described (2).

Comparisons of hemoximeters from leading manufacturers, which are intended for use as reference procedures, have not been published. The hemoximeters of the companies participating in the present study were introduced in papers dealing with the reference analysis of pulse oximeters (3–9).

For pulse oximeter calibration and confirmation tests done on volunteers, the United States Food and Drug Administration (FDA) requires only one CO-oximeter

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Hartmut Gehring, MD, is the head of the Laboratory for Controlled Hypoxemia Studies (CHS). Testing and calibrating of the pulse oximeter is the essential task of this laboratory.

The study with the volunteers was performed at the request of, and financially supported by, a pulse oximeter manufacturer.

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Table 1. Manufacturers Included in the Study with Serial Numbers of the Devices A and B

Abbr.	Manufacturer	Device	Serial-no.: A	Serial-no.: B
RA	Radiometer	ABL 735	52314	52310
NO	Nova Biomedical	STP CCX 1	Y02A03070	Y02703060
IL	Instrumentation Laboratory*	682 CO-Oximeter	R03101115	R371200699
	Instrumentation Laboratory*	GEM Premier 3000	15381	15087
BA	Bayer Diagnostics	Rapidlab 860	7790	7720
RO	Roche	OMNI S	1558	1503

* In the use of one device.

Table 2. Measurement Principles of the Hemoximeter

Manufacturer	Device	Technical note
RA	ABL 735	Blood hemolysis with ultrasound 128 wavelengths sample volume ~100 μL
NO	STP CCX 1	Blood hemolysis with ultrasound 7 wavelengths; conductivity (ctHb) sample volume ~150 μL
IL	682	Chemical blood hemolysis 6 wavelengths sample volume ~150 μL
BA	860 Rapidlab	Blood hemolysis with ultrasound selection of 37 in 256 wavelengths sample volume ~150 μL
RO	OMNI S	Blood hemolysis with ultrasound 520 wavelengths sample volume ~110 μL

device for measuring sO_2 used according to the hemoximeter manufacturer's recommended procedures and supplies (1).

Bland and Altman pointed out that not just test devices but also reference devices produce errors (10). The Bland–Altman procedure for error analysis and presentation is useful for the presentation of pulse oximeter accuracy data (11).

The objective of this study was to determine the measurement error associated with the determination of arterial oxygen-saturation by hemoximetry.

Because no reference procedure is available for measuring oxygen saturation with CO-oximeters, the pairwise differences between identical devices from five leading manufacturers, as well as the differences between manufacturers, were assessed in order to estimate the error between the hemoximeters.

METHODS

Device Preparation

Table 1 lists the participating companies as well as the serial numbers and model descriptions of the devices. Table 2 describes the technical measurement procedure. All devices were assembled pairwise in a climatically controlled room and serviced by employees from the manufacturer before they were put into operation. The air pressure gauges integrated within the devices were checked and synchronized with the reference system (http://193.175.120.23/an/pt/solar/wetter/werte.htm). During monitoring phases, the prevailing air pressure values were recorded hourly. The devices were adjusted so that they reported identical units and denotations of the variables.

The amount of blood required to provide sufficient material for the entire range of blood gas analyzers was tested under several conditions. At least three syringes specially designed for blood gas sampling (PICO™ 50 with dry electrolyte-balanced heparin (80 IU, Radiometer Copenhagen)), and filled with 2 mL of blood, appeared sufficient to provide all systems with an adequate amount of blood.

Study Protocol

A set up was chosen for the study which

1. reflected the reality for the operation or the intensive care unit with blood gas analyses from patients, and
2. also corresponded to the standards of the desaturation studies for the testing and calibration of pulse oximeters.

Twelve healthy male and female volunteers were investigated over 4 days regarding standardized calibration procedures for pulse oximeters corresponding to the requirements of the FDA over the range of 70%–100% sO_2. The study was approved by the Ethical Committee of the University of Luebeck, Germany, and all participants gave written informed consent. All volunteers breathed an oxygen/nitrogen mixture with high flow (15 L/min) given by a Trajan 808™ (Draeger Medical, Luebeck) via a valve-less face mask. Three N-3000 with finger clip and one N-595 with a

forehead sensor (all Nellcor, Pleasanton, CA) served as reference pulse oximeters for breathe down control. Mean values, as well as individual data points from the systems, were presented continuously on a display. The protocol followed the standard procedure of the FDA (1) where five levels (L) were established in the sO_2 range between 100% and 70%, and five blood samples were withdrawn under steady state plateau conditions for testing, with the hemoximeter at the breathe-down laboratory (2 OSM 3 and 2 ABL 725, Radiometer Copenhagen, Denmark). At the end of three of the levels (L_{97} near to 97% sO_2, L_{85} at 85% sO_2 and L_{75} at 75% sO_2) and also under the presence of plateau conditions, three syringes were rapidly filled representing the sample for one level. The breathe-down procedure was repeated, so that at least six sampling points materialized for each volunteer. The three syringes marked only with a colored spot were mixed and then transferred within 30 s to the adjacent study laboratory. Three technical assistants, blinded to the syringes, were randomly assigned to a manufacturer and the Devices A or B for testing. Data from each blood gas analyzer were stored on disk and in printed form before they were transferred to an Excel™ data file.

Statistical Analysis

It should be remembered that 1) each device received blood that was randomly selected from a sample, and that 2) there was no value for the true saturation.

The variables sO_2 (hemoglobin oxygen saturation), cO_2Hb (oxygen content of hemoglobin), cHHb (deoxyhemoglobin concentration), cCOHb (carboxyhemoglobin content), cMetHb (methemoglobin content), and ctHb (total hemoglobin content) were analyzed. The basis for evaluation were the raw data and the differences between the Devices A and B related to level, considering session, subject, manufacturer, and device.

The measurements are modeled as:

$$Y_{ijklm} = M_{ijk} + \Delta_{jlm} + \varepsilon_{ijklm}$$

With $i = 1, 2$: session; $j = 1, 2, 3$: level; $k = 1, \ldots, 12$: subject; $l = 1, \ldots, 5$: manufacturer; $m = 1, 2$: device.

Here M_{ijk} is a randomized effect depending on session, level, and subject, Δ_{jlm} is an effect depending on level, manufacturer and device, and ε_{ijklm} is a measurement error with the expected value 0 and standard deviation σ_{jl}, depending on level and manufacturer.

The Wilcoxon signed rank sum tests with Bonferroni-Holm adjustment were applied to calculate P values for differences of devices and differences between manufacturers. See also Appendix A.

The question regarding which variable was responsible for the increasing errors in sO_2 measurements with respect to levels 97, 85, and 75 was answered by analysis of variance proportion. The procedure for analyzing the proportion of the variance of cHHb and cO_2Hb that contributed to the variance of the sO_2 measurements is listed in Appendix B.

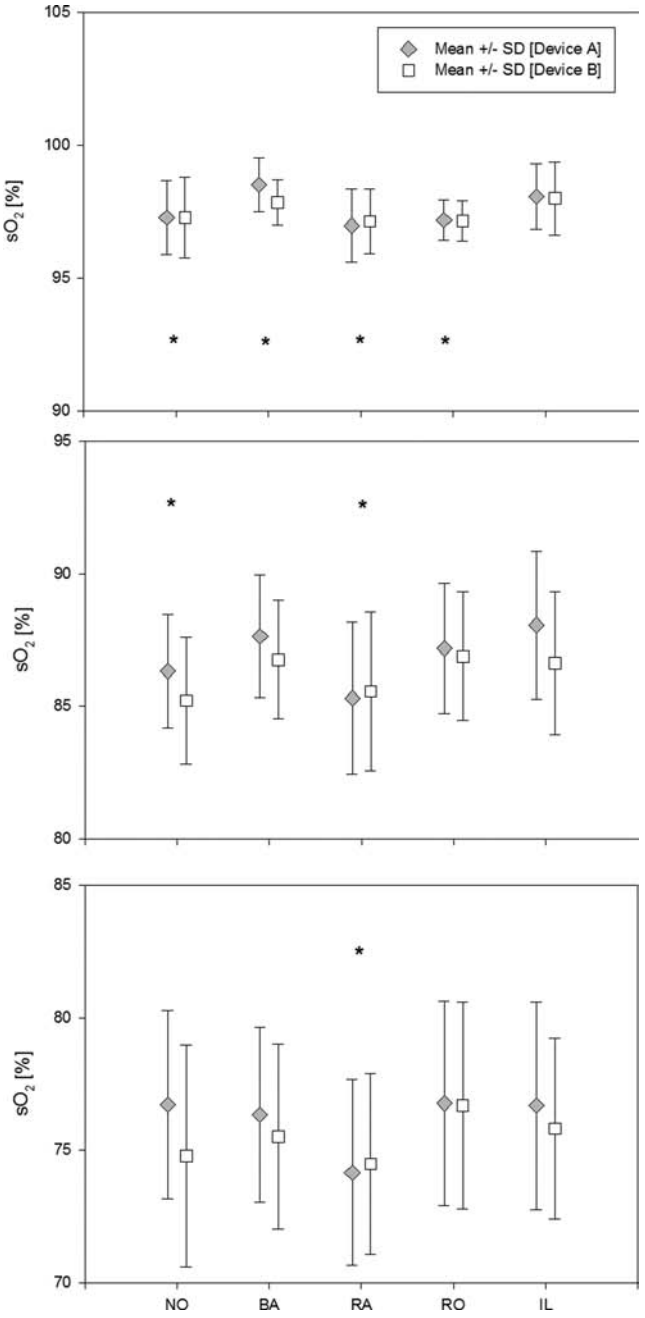

Figure 1. Mean and SD of the absolute values, summarized for Sessions 1 and 2. *$P < 0.05$; test between Group 1 (mean of Devices A and B) versus Group 2 (mean of the other companies).

RESULTS

Each of the test systems was used to analyze $n = 72$ samples. The distribution of the absolute values for the individual manufacturers is given in Figure 1. The significances listed for level 97 between the mean values of the two Devices A and B from one manufacturer, compared with the mean value from all other companies were masked by the increasing variances at levels 85 and 75.

The measured differences, pairwise, between Devices A and B, as a measure for the error of the hemoximeters within a series increased clearly and

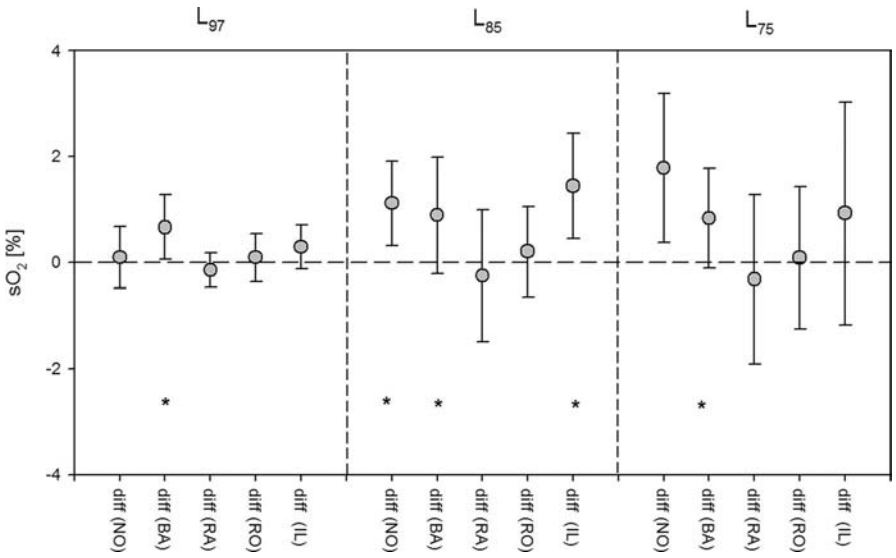

Figure 2. Mean and SD of the differences of the devices (A–B) of each company, ordered to level, summarized for Sessions 1 and 2. $P < 0.05$; test between Devices A and B.

Table 3. Differences Between Devices (A–B) for Five Manufacturers

	NO	BA	RA	RO	IL
sO_2 (%)					
Mean	0.95	0.80	−0.24	0.09	0.76
SD	0.43	0.47	0.37	0.38	0.70
CI	[0.67 to 1.22]	[0.51 to 1.10]	[−0.47 to 0.00]	[−0.15 to 0.33]	[0.32 to 1.20]
cHHb (%)					
Mean	−0.26	−0.94	0.29	−0.07	−0.85
SD	0.31	0.51	0.36	0.36	0.65
CI	[−0.46 to −0.07]	[−1.26 to −0.61]	[0.06 to 0.52]	[−0.30 to 0.16]	[−1.28 to −0.41]
cO_2Hb (%)					
Mean	1.19	−0.15	0.06	0.14	0.00
SD	0.27	0.51	0.35	0.38	1.18
CI	[1.02 to 1.36]	[−0.48 to 0.17]	[−0.16 to 0.28]	[−0.10 to 0.37]	[−0.75 to 0.74]
cO_2Hb + cHHb (%)					
Mean	0.94	−1.07	0.36	0.06	−0.84
SD	0.26	0.69	0.09	0.04	0.97
CI	[0.78 to 1.11]	[−1.50 to −0.64]	[0.31 to 0.42]	[0.04 to 0.09]	[−1.49 to −0.18]
cCOHb (%)					
Mean	−0.94	1.21	−0.14	−0.01	0.50
SD	0.18	0.73	0.06	0.08	0.82
CI	[−1.06 to −0.83]	[0.75 to 1.68]	[−0.18 to −0.11]	[−0.06 to 0.04]	[−0.20 to 1.02]
cMetHb (%)					
Mean	0.01	−0.15	−0.21	−0.10	0.12
SD	0.12	0.07	0.08	0.03	0.28
CI	[−0.07 to 0.09]	[−0.20 to −0.10]	[−0.27 to −0.16]	[−0.12 to −0.07]	[−0.31 to −0.06]
ctHb (g/dL)					
Mean	−0.77	−0.29	0.00	−0.39	0.38
SD	0.29	0.19	0.06	0.81	1.18
CI	[−0.95 to −0.59]	[−0.42, to −0.17]	[−0.04 to 0.03]	[−0.91 to 0.11]	[−0.37 to 1.13]

Summarized data of Sessions 1 and 2 and on levels 95, 85, and 75 % sO_2.

sO_2 = hemoglobin oxygen saturation; cO_2Hb = oxygen concentration of hemoglobin; cHHb = deoxyhemoglobin concentration; cCOHb = carboxyhemoglobin concentration; cMetHb = methemoglobin concentration; ctHb = total hemoglobin concentration.

significantly with all manufacturers between levels 97 and 85. This effect was even stronger between level 97 and 75 (Fig. 2).

Summarized for all samples, the differences of the Devices A and B were recorded as means and standard deviations for each manufacturer in Table 3, completed with the values for cHHb and cO_2Hb as well as the sums of cO_2Hb and cHHb representing the denominator of the formula $sO_2 = cO_2Hb/(cO_2Hb + cHHb)$.

The measurement of cCOHb showed no dependence on sO_2 level or session, but revealed significant differences between the manufacturers, as well as between the Devices A and B (Table 3). Overall, the absolute measured values for cCOHb were scattered over a broad range between 0% and 4%.

The measurement of cMetHb also showed no dependence with regard to sO_2 level and session, but here, just as with cCOHb, significant differences were

Table. 4. Variance Proportion Test. See Appendix B for Abbreviations

Level	$\hat{\mu}_{cHHb}$	$\hat{\mu}_{cO_2Hb}$	$\hat{\sigma}_{cHHb}$	$\hat{\sigma}_{cO_2Hb}$	VP_{cO_2Hb}	VP_{cHHb}
75%	23.34	74.94	3.47	3.44	0.09	0.91
85%	12.61	85.64	2.49	2.37	0.02	0.98
97%	2.06	96.21	0.83	0.89	0.00	1.00

seen between the manufacturers as well as between the Devices A and B (Table 3). Overall, the scattering of the measured values was restricted to a narrow range of between 0% and 1% cMetHb.

The variances associated with the measurement of cHHb were disproportionately responsible for the increasing differences between Devices A and B (Table 4).

DISCUSSION

For all manufacturers, the differences of the sO_2 values, measured with identical devices of a series, increase as saturation falls. For the analysis of sO_2, one can therefore assume that a measurement error also exists even for the "gold standard" of hemoximetry, and that this will influence pulse oximeter calibration.

For the absolute values, significant differences between the instrument manufacturers already occurred at level 97, an effect that was masked by the increasing variance at levels 85 and 75. The variance for the measurement of cHHb can be identified as an important cause underlying the error. The measurement errors for cMetHb were significant, but restricted to a range of 0%–1%. However, there were significant variances in the measurement error of cCOHb between 0% and 4%.

A standardized production of blood samples with a defined saturation level between 0% and 100% can only be achieved in isolated cases using a tonometrically based gravimetric procedure (2). A primary calibration can only occur in the factory before the devices are shipped to the customer. Any further calibration is then based merely on the application of aqueous sample materials; therefore, a fundamental determination of the measurement error is not possible. In particular, the error due to an inadequate hemolysis of the cellular substances in the blood is lost when calibrating with the aqueous samples.

As a possible means for approaching the unknown values for the true sO_2 levels, laboratories involved in calibrating pulse oximeters use several hemoximeters of an identical design from one or several companies, and then compute mean values (12) from them. This assumption is based, however, on a randomly distributed error that becomes minimized upon averaging.

The study presented here was based on the fact that all test devices received randomized blood from a population sample. In order to test for reproducibility, the breathe down procedure was carried out twice for each test subject (Sessions 1 and 2). In the statistical analysis, an effect based on differences between Sessions 1 and 2 could be excluded.

Considering the results presented, we can also assume a marked error within the reference devices. This is an effect that was already clearly identified by Bland and Altman, a fact which led them to establish their own evaluation procedure (10). A modified presentation, related only to the values obtained from the reference devices (11), can therefore be recommended only with reservations.

The algorithms and corrective procedures established by the manufacturers represent a further gray zone as regards to the reporting of measurements within the reference systems. As a single example, the number of wavelengths used in the devices investigated clearly varies between the different manufacturers (Table 2).

The variable sO_2 reported by the hemoximeters refers to the functional oxygen saturation. The calculation is based on hemoglobin that can bind oxygen (functional $sO_2 = cO_2Hb/(cO_2Hb + cHHb)$ and is directly comparable to the value reported by the pulse oximeters. A new pulse oximeter (12) is now also able to measure cMetHb and cCOHb so that, in principle, a measurement of the fractional oxygen saturation (fractional $sO_2 = cO_2Hb/(cMetHb + cCOHb + cO_2Hb + cHHb)$ is also possible by pulse oximetry. In a paper by Barker et al. (12), a Bland-Altman calculated difference (bias) of −1.12% and a precision of ±2.19% was reported for the cCOHb pulse oximetric value. This represents an order of magnitude that was also measured in the present test with the reference devices.

A fundamental problem is the lack of uniformity in the nomenclature used by the different manufacturers for the reported variables. Only the measurement of functional oxygen-saturation (sO_2 in %) was applied uniformly both for the hemoximeter and the pulse oximeter. The term "fractional oxygen saturation" will find increasing use due to the application of the new pulse oximeters in clinical settings. Errors arising from different spellings and definitions are more or less inevitable. In Germany, a consensus-building conference involving the leading manufacturers of blood gas analysis devices has already taken place, the results of which were published in the "Qualitest Consensus" (13).

At the time when the testing was performed, the devices examined were state-of-the-art. New developments in oximeter testing and standardization are desirable. A standardized test procedure for hemoximeters is important for the variables sO_2, cO_2Hb, cHHb, cCOHb, and cMetHb, similar to those already established for the measurement of ctHb (14).

CONCLUSIONS

Errors in hemoximeter determination of sO_2 depend both on the manufacturer of the hemoximeter as well as the sO_2 range. The variable cHHb disproportionately contributes to the measurement error for sO_2. Further, the measurement error for cCOHb is related to the absolute values and the variance is

clearly greater than is the case for cMetHb, a fact relevant to calculating the fractional saturation.

Finally, we strongly recommended the Bland and Altman procedure as the preferred analysis method for reporting and presenting hemoximeter errors.

APPENDIX A: STATISTICAL TESTS AND CONFIDENCE INTERVALS

Estimators and Confidence Intervals for Single Standard Deviations σ_{jl}

We assume that the differences

$$D_{ijkl} = Y_{ijkl1} - Y_{ijkl1} = \Delta_{ijkl1} - \Delta_{ijkl2} + \varepsilon_{ijkl1} - \varepsilon_{ijkl2}$$

are distributed according to $N(\Delta_{ijkl1} - \Delta_{ijkl2}, 2\sigma_{jl}^2)$, apart from a small fraction of outliers, whereby $\Delta_{ijkl1} - \Delta_{ijkl2}$ is the systematic difference between two identical devices. (Note that the effect M_{ijk} disappears here.) Denoting the available differences D_{ijkl} for given level j and manufacturer l with $D_1, D_2, \ldots, D_n$, conventional parametric confidence intervals for σ_{jl} are then given by

$$\left[\sqrt{\frac{\sum_{a=1}^{n}(D_a - D_\bullet)^2}{2\chi^2_{n-1;1-\alpha/2}}}, \sqrt{\frac{\sum_{a=1}^{n}(D_a - D_\bullet)^2}{2\chi^2_{n-1;\alpha/2}}}\right]. \qquad [1]$$

Here $\chi^2_{m;\beta}$ denotes the β-quantile of the χ^2 distribution with m degrees of freedom.

To safeguard against outliers and obtain a robust estimate for σ_{jl}, we deleted the smallest and largest differences D_a. For this purpose, one has to replace the χ^2 quantiles in Eq. [A1] with new quantiles taking into account this trimming. The latter have been determined using extensive Monte-Carlo simulations. Using the 50% quantile, we also calculated a robust point estimator for σ_{jl}, i.e., a "trimmed version" of

$$\sqrt{\frac{\sum_{a=1}^{n}(D_a - D_\bullet)^2}{2\chi^2_{n-1;0.5}}}.$$

Confidence Intervals for Ratios σ_{cl}/σ_{bl}

For $1 \le b < c \le 3$, a standard $(1 - \alpha)$ -confidence interval for the ratio σ_{cl}/σ_{bl} is given by

$$\left[\frac{\hat{\sigma}_{cl}/\hat{\sigma}_{bl}}{\sqrt{F_{n(c)-1,\,n(b)-1;1-\alpha/2}}}, \frac{\hat{\sigma}_{cl}/\hat{\sigma}_{bl}}{\sqrt{F_{n(c)-1,\,n(b)-1;\alpha/2}}}\right].$$

Here $F_{m[1],m[2];\beta}$ denotes the β-quantile of Fisher's F distribution with $m(1)$ and $m(2)$ degrees of freedom, and

$$\hat{\sigma}_{jl} := \sqrt{\frac{\sum_{a=1}^{n(j)}(D_a^{jl} - D_\bullet^{jl})^2}{2(n(j)-1)}}$$

is the usual estimator of σ_{jl} based on all $n(j)$ available differences $D_a^{jl} = D_{ijkl}$.

Again we modified this classical procedure by means of trimmed samples and corresponding surrogates for the F quantiles.

Statistical Inference About the Device Differences $\Delta_{ijkl1} - \Delta_{ijkl2}$

The null hypothesis that "$\Delta_{ijkl1} - \Delta_{ijkl2} = 0$", i.e., there is no systematic difference between the two devices of manufacturer l at level j, was tested via Wilcoxon's signed rank test. Using Wilcoxon's signed rank test rather than a corresponding t-test has the advantage that the results are less sensitive to outliers, and one could even relax the model assumptions considerably. Since we are testing 15 null hypotheses simultaneously (5 manufacturers, 3 levels), we adjusted our P values via the Bonferroni–Holm procedure (15).

With $D_1, D_2, \ldots, D_n$ as in "Estimators and Confidence Intervals for Single Standard Deviations σ_{jl}" section, a $(1 - \alpha)$-confidence interval for $\Delta_{ijkl1} - \Delta_{ijkl2}$ consists of all numbers δ such that the Wilcoxon signed rank statistic $W(D_1 - \delta, D_2 - \delta, \ldots, D_n - \delta)$ lies within the thresholds for the two-sided Wilcoxon's signed rank test at level α. In other words, we determine the set of all values δ such that the latter test does *not* reject the null hypothesis "$\Delta_{ijkl1} - \Delta_{ijkl2} = \delta$".

Comparing Manufacturers

To test whether the devices of manufacturer l are significantly different from the other manufacturer's devices at a certain level j, we considered the means

$$Y_{ijkl} = (Y_{ijkl1} + Y_{ijkl2})/2 = M_{ijk} + \Delta_{jl} + \varepsilon_{ijkl}$$

over two identical devices with $\Delta_{jl} = (\Delta_{jl1} + \Delta_{jl2})/2$ describing the average effect of manufacturer l at level j and $\varepsilon_{ijkl} = (\varepsilon_{ijkl1} + \varepsilon_{ijkl2})/2$ having mean zero and standard deviation $\sigma_{jl}/\sqrt{2}$. Now we considered the differences

$$D_{ijkl} = Y_{ijkl} - \bar{Y}_{ijkl} = \Delta_{ijkl} - \bar{\Delta}_{ijkl} + \varepsilon_{ijkl} - \bar{\varepsilon}_{ijkl},$$

where the bar stands for averaging over the remaining four manufacturers. With these differences we tested the 15 null hypotheses "$\Delta_{ijkl} = \bar{\Delta}_{ijkl}$" via Wilcoxon's signed rank test plus Bonferroni–Holm adjustment, analogously as in "Statistical Inference About the Device Differences $\Delta_{ijkl1} - \bar{\Delta}_{ijkl2}$" section.

APPENDIX B: VARIANCE PROPORTIONS

Our aim is to quantify the contribution of errors in cO_2Hb and cHHb measurements to the total error in measuring sO_2. To this end, we model the former measurements as $cO_2Hb = \mu_1 + \varepsilon_1$ and $cHHb = \mu_2 + \varepsilon_2$ with true concentrations μ_1, μ_2 and independent random errors ε_1, ε_2 having mean zero and standard deviations σ_1, σ_2. Assuming that

$\sigma_1 + \sigma_2 << \mu_1 + \mu_2$, we may expand sO_2 as follows:

$$sO_2 = \frac{cO_2Hb}{cO_2Hb + cHHb} = \frac{\mu_1 + \varepsilon_1}{\mu_1 + \mu_2 + \varepsilon_1 + \varepsilon_2}$$

$$= \frac{\mu_1}{\mu_1 + \mu_2} + \frac{\mu_2\varepsilon_1 - \mu_1\varepsilon_2}{(\mu_1 + \mu_2)(\mu_1 + \mu_2 + \varepsilon_1 + \varepsilon_2)}$$

$$\approx \frac{\mu_1}{\mu_1 + \mu_2} + \frac{\mu_2\varepsilon_1 - \mu_1\varepsilon_2}{(\mu_1 + \mu_2)^2}.$$

The second summand on the right hand side has variance

$$\frac{\mu_2^2\sigma_1^2 + \mu_1^2\sigma_2^2}{(\mu_1 + \mu_2)^4}.$$

Thus, the variance proportion (VP) of cO_2Hb, i.e., the contribution to the overall variance of sO_2 is essentially equal to

$$VP_{cO_2Hb} = \frac{\mu_2^2\sigma_1^2}{\mu_2^2\sigma_1^2 + \mu_1^2\sigma_2^2}.$$

To obtain an estimate for this variance proportion, we plug in classical estimates for the unknown means μ_i and standard deviations σ_i based on all measurements from a certain level. That means, we average over all test subjects, sessions, manufacturers, and devices. This leads to $\hat{V}P_{cO_2Hb} = \hat{\mu}_2^2\hat{\sigma}_1^2/(\hat{\mu}_2^2\hat{\sigma}_1^2 + \hat{\mu}_1^2\hat{\sigma}_2^2)$.

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Photoplethysmography: Beyond the Calculation of Arterial Oxygen Saturation and Heart Rate

Kirk H. Shelley, MD, PhD

In this article, I examine the source of the photoplethysmograph (PPG), as well as methods of investigation, with an emphasize on amplitude, rhythm, and pulse analysis. The PPG waveform was first described in the 1930s. Although considered an interesting ancillary monitor, the "pulse waveform" never underwent intensive investigation. Its importance in clinical medicine was greatly increased with the introduction of the pulse oximeter into routine clinical care in the 1980s. Its waveform is now commonly displayed in the clinical setting. Active research efforts are beginning to demonstrate a utility beyond oxygen saturation and heart rate determination. Future trends are being heavily influenced by modern digital signal processing, which is allowing a re-examination of this ubiquitous waveform. Key to unlocking the potential of this waveform is an unfettered access to the raw signal, combined with standardization of its presentation, and methods of analysis. In the long run, we need to learn how to consistently quantify the characteristics of the PPG in such a way as to allow the results from research efforts be translated into clinically useful devices.

(Anesth Analg 2007;105:S31–6)

The photoplethysmograph (PPG) waveform was studied and used clinically long before the discovery of its utility in the calculation of arterial oxygen saturation (1,2). That discovery had such a profound impact on clinical monitoring that the other potential uses of the waveform quickly faded from the attention of clinicians. This neglect of the waveform was accentuated by its absence from the early stand-alone pulse oximeter devices. The pulse was indicated by either a bouncing bar or flashing heart symbol.

My personal introduction to this waveform was during my anesthesiology residency in the late 1980s. Already trained as a critical care provider (internal medicine), I found the opportunity to observe clinical waveforms during surgery fascinating. During my residency, a new clinical monitoring system was purchased and thus I observed for the first time the plethysmographic waveform. One fateful day, I asked one of the senior faculty "What does the waveform mean?" pointing to the plethysmograph displayed below the electrocardiogram. His answer . . . "That means your pulse oximeter is working." Undeterred I first looked in a standard anesthesiology textbook, and then in a textbook of monitoring. I could find no mention of this "new" waveform.

The rest of this article will outline what I have found during my investigations, both of the literature and experimentally. I have been fortunate that my interest occurred during a period of remarkable growth in computational power (critical to both waveform analysis and literature searches) and an improved understanding of digital signal processing. My ultimate conclusion is that we have only just begun to tap the potential of this remarkable waveform (3). This article was created as part of the International Symposium on Innovations and Advancements in Monitoring Oxygenation and Ventilation (ISIAMOV) 2007 Supplement to *Anesthesia &Analgesia*. The topic (Photoplethysmography: Beyond the Calculation of Arterial Oxygen Saturation and Heart Rate) matches the material presented at the symposium that took place at Duke University, Durham, NC during March 2007.

SOURCE OF THE WAVEFORM

Beer's law of light describes the elements that contribute to the pulse oximeter waveform.

$$A_{total} = E_1C_1L_1 + E_2C_2L_2 + \ldots E_nC_nL_n$$

Where,

A_{total} = absorption at a given wavelength
E_n = extinction coefficient (absorbency)
C_n = concentration
L_n = path length

Conceptually, it is most useful to view the pulse oximeter waveform as measuring the change in blood

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Table 1. Desirable Characteristics for a Pulse Oximeter Used for Waveform Analysis

- Waveform display
  - Ability to change time scales
  - Switch between scroll and "erase bar" display modes
  - Wavelength selectable (IR versus red versus other)
- Ability to turn off auto-gain function
- Ability to turn off auto-center function
- Ability to set the amplitude gain
- Numeric display of amplitude and DC signal
- Ability to use a wide range of probes (finger, ear and reflective)
- Digital and analog outputs of pulse oximeter waveform for capture by data collection equipment

No pulse oximeter commercially available has this combination of characteristics.

Table 2. Factors Affecting Pulse Oximeter Waveform Amplitude

- Increased amplitude due to vasodilatation
  1. Pharmacological—nitroprusside
  2. Physiologic—warming, sedation
  3. Anesthetic—regional sympathetic blocks (spinal and epidural)
- Decreased amplitude due to vasoconstriction
  1. Pharmacological—phenylephrine, ephedrine
  2. Physiologic—cold, surgical stress

volume (more specifically path length), during a cardiac cycle, in the region being studied (typically the fingertip or earlobe). The general consensus is that the waveform comes from the site of maximum pulsation within the arteriolar vessels where pulsatile energy is converted to smooth flow just before the level of the capillaries (4,5). Even this fundamental understanding is not without controversy, as demonstrated in an article by Kim et al. (6) in which they hypothesized that the source of the signal is from "open arteriovenous anastomoses in the cutaneous circulation."

The PPG is a remarkably simple device consisting of a light source (most commonly an LED) and light detector (photo diode). The detector can be placed either directly across from the light source for transmission plethysmography or next to the light source for reflective plethysmography. The plethysmographic waveform that is displayed on the commercial pulse oximeter is a highly processed and filtered signal. As pointed out in a recent editorial (7), when attempting to use clinical monitoring devices as research devices one must learn how to cope with proprietary filters and algorithms. It is hoped that, encouraged by articles like this one, equipment manufacturers will consider adding features that will allow their devices a broader range of use (Table 1). At the present time the literature consists largely of an anecdotal mass of what are essentially case reports, combined with a few small prospective and retrospective studies attempting to extract new clinical information from the PPG. Key to unlocking the potential of this waveform is unfettered access to the raw signal, combined with standardization of its presentation and methods of analysis. In the long run, we need to learn how to consistently quantify the characteristics of the PPG in such a way as to allow the results from research efforts be translated into clinically useful devices.

Of the two or more wavelengths measured by the pulse oximeter, traditionally only the infrared signal (approximately 940 nm) is presented. The information from this wavelength is displayed because it is more stable over time, especially when compared to the red signal (660 nm), which is more susceptible to changes in the oxygen saturation. In addition, only the pulsatile component or AC portion is displayed. The static component or DC (created mostly by the absorption of light by surrounding tissue) is eliminated by an auto-centering routine used to ensure the waveform remains on the display screen. With changes in the degree of venous congestion, the waveform can be noted to drift partly off the screen and then return via the auto-centering algorithm.

All clinical pulse oximeters that display a plethysmographic waveform do so with an auto-gain function designed to maximize the size of the waveform displayed. Some manufacturers include an option to turn off this automatic resizing function. Without this option it would be impossible to analyze the amplitude of the pulse oximeter waveform, an important parameter to measure, when analyzing the waveform. When examining the PPG amplitude change over time, the region of the body being measured is important. In the finger, where the walls of the cutaneous vessels are richly innervated by a-adrenoceptors, the sensitivity to changes in the sympathetic system are greater than when compared to other areas of the body such as the earlobe (8).

At this time, no calibration procedure is known to standardize the PPG amplitude for comparing one patient waveform to another. Note, this is an important issue and an excellent research opportunity. The signal is therefore not given a unit designation. Similar to central venous pressure measurement, the value of the plethysmograph comes from an analysis over time, as opposed to any absolute number. The term "plethysmograph" is derived from the Greek root "plethysmos" meaning "to increase." There is a close correlation ($r = 0.9$) between the PPG and the more traditional strain gauge plethysmograph (4).

AMPLITUDE ANALYSIS

One of the more useful plethysmographic features is the waveform amplitude (Table 2). Amplitude changes can be concealed by the auto-gain function found on most pulse oximeters. By turning off the auto-gain, certain observations can be made. For example, over a remarkably wide range of cardiac output, the amplitude of the plethysmograph signal is directly proportional to the vascular distensibility (9). If the vascular compliance is low, for example during episodes of increased sympathetic tone, the pulse

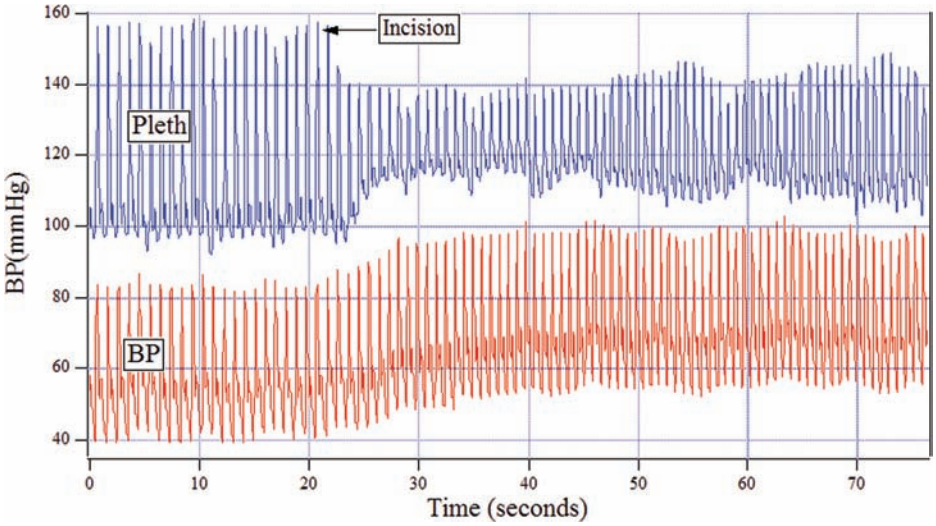

Figure 1. Response of the pulse oximeter waveform (Pleth) to surgical stimulation. In this case, a patient undergoing general anesthesia experiences the first surgical incision of an operative procedure. The pulse oximeter waveform is noteworthy for the sudden reduction in amplitude. This is felt to be indicative of a sudden increase in sympathetic tone causing peripheral vasoconstriction. A concomitant increase in the arterial blood pressure (BP) supports this explanation.

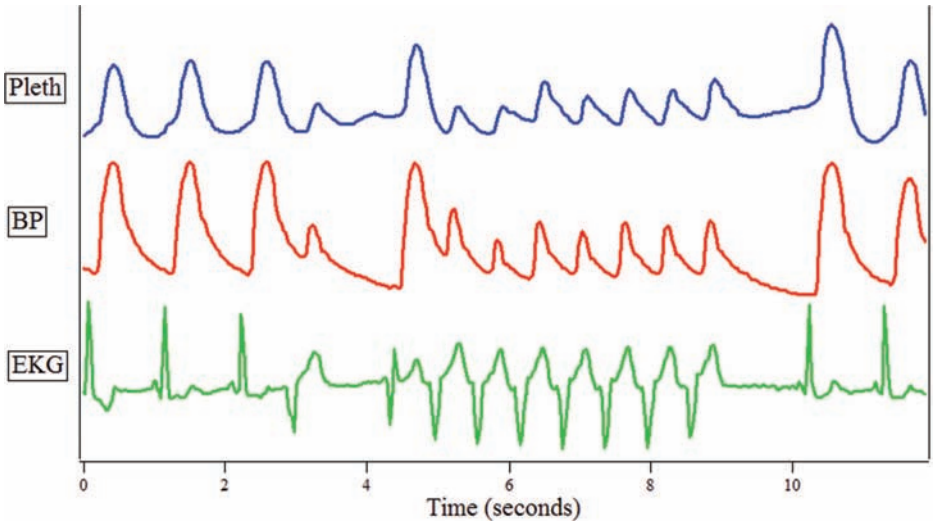

Figure 2. The impact of ventricular tachycardia on the pulse oximeter waveform (Pleth), arterial pressure waveform (BP), and electrocardiogram (ECG). The sudden reduction in the amplitude of the pulse oximeter waveform, combined with the typical ECG pattern, should give important warning regarding the presence of a dangerous situation.

oximeter waveform amplitude is also low. With vasodilatation, the pulse oximeter waveform amplitude is increased. One should never confuse a large pulse amplitude with the presence of high arterial blood pressure nor *vice versa*. It is not unusual for the pulse oximeter waveform amplitude to decrease during significant increases in arterial blood pressure that are due to increase sympathetic tone.

Once a baseline measurement has been established, the pulse oximeter amplitude can be followed as a gauge of sympathetic tone (10–12). An intriguing potential use of the plethysmograph may be as a indicator of MAC-BAR (13), the dose of anesthetic required to block adrenergic response in 50% of individuals who have a surgical skin incision. The degree of sympathetic responsiveness a patient retains during an anesthetic might have important clinical implications (Fig. 1). This may be particularly true in patients with a compromised coronary circulation, where dramatic shifts in the hemodynamic status should be avoided. This is an area in which further research efforts would be useful.

RHYTHM ANALYSIS

As can be seen in Figure 2, the pulse oximeter waveform can be a useful tool for detecting and diagnosing cardiac arrhythmias (14). To be used to maximum benefit, the pulse oximeter waveform is used in conjunction with the electrocardiogram. This can greatly help in correctly interpreting artifacts due to patient movement or electrical cautery. As demonstrated in these figures, the pulse oximeter waveform morphology is related to the arterial blood pressure waveform (15). As expected after each premature ventricular beat, there is a compensatory pause, which

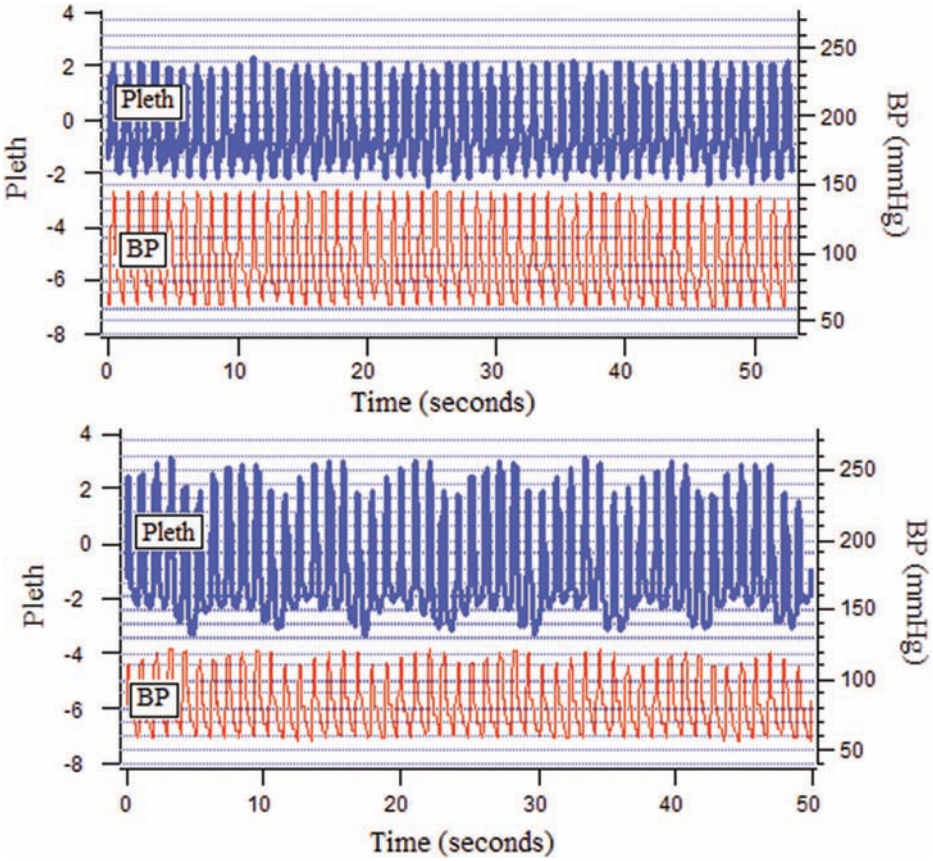

Figure 3. The effect of blood loss on the pulse oximeter waveform (Pleth) and arterial pressure waveform (BP). The upper diagram shows the baseline waveforms of the patient under general anesthesia with positive pressure ventilation. The lower diagram is after a 1000 mL blood loss. The effect of positive pressure ventilation is apparent.

gives more time for the ventricle to fill. The next normal heartbeat is, therefore, associated with an increase in stoke volume. This is reflected in an increase of arterial blood pressure. It is thought that the same mechanism accounts for an increase in the size of the pulse oximeter amplitude after a compensatory pause. A beat-to-beat change of the pulse oximeter amplitude is often the first clue that the patient has developed an irregular heart rhythm. Comparing the pulse oximeter waveform to the electrocardiogram is an excellent way to confirm these changes.

PULSE ANALYSIS

A number of unanticipated uses of the pulse oximeter have been developed by clinicians. Most of these uses depend on the ability of the pulse oximeter to detect arterial pulsation. These applications take advantage of the fact that the PPG is remarkably sensitive to pulsatile blood flow.

One clever use of the pulse oximeter has been the determination of systolic blood pressure. This is done by taking advantage of the pulse oximeter's ability to detect a peripheral pulse. The pressure at which the pulse is detected corresponds closely to the systolic blood pressure (16–18). This technique is helpful in noisy environments, or with neonates in which the use of stethoscope would be difficult. The complex relationship between arterial blood pressure and the volumetric nature of the PPG has complicated the search for the noninvasive beat-to-beat measurements desired by clinicians (15,19). It is hoped that standardization of the equipment, and better understanding of the underlying physiology of the PPG, may allow for obtaining this elusive goal in the future.

A number of studies have been published using the pulse oximeter's plethysmographic capability to detect tissue perfusion. The advantage the pulse oximeter offers is the ability to do noninvasive, continuous monitoring of peripheral blood flow with readily available technology. Using either transmission or reflective plethysmographic techniques, a number of tissues have been studied. The traditional pulse oximeter depends on transmission plethysmography, with the light taking a direct path through the tissue being studied (i.e., the fingertip or earlobe). Reflective plethysmography takes advantage of the back-scattering of light to the surface (i.e., forehead). Published studies using these techniques to determine tissue perfusion have been performed on small bowel (20), reimplanted fingers (21), and free flaps (22).

RESPIRATORY VARIABILITY ANALYSIS

With ventilation (spontaneous and positive pressure) there is fluctuation of both the baseline (D/C) and pulsatile (A/C) components of the plethysmographic waveform. The ability to detect the influence of the respiratory system on the cardiovascular system opens intriguing possibilities. At the minimum, it is believed that the respiratory rate can be reliably determined using the plethysmographic waveform (23–27).

The effect of positive pressure ventilation on the arterial pressure waveform has been well described (28). It is theorized that with each positive pressure breath venous return to the heart is impeded resulting in a temporary reduction in cardiac output. As a patient becomes volume depleted, with a resulting decrease in venous pressure, positive pressure ventilation has an exaggerated impact on the arterial blood pressure. A similar effect on the plethysmograph has been described (29,30). Figure 3 demonstrates this phenomenon. Monitoring the respiratory variability seen in the pulse oximeter waveform may be a useful method of detecting occult hemorrhage, with its resulting hypovolemia (31,32). There are ongoing research efforts designed to find the best site and method of analysis for quantifying the effects of ventilation on the plethysmographic waveform (33,34).

THE PATH FORWARD

The availability of increasingly powerful methods of digital signal processing are allowing for a renaissance in the field of PPG research. Calculations that once required mainframe computers are now performed almost instantaneously with digital signal processing chips. This has allowed for the detailed re-examination of the plethysmograph. Combined with improved understanding of the underlying physiology of the waveform it is easy to predict the emergence of multifunction pulse oximeters.

To uncover the true potential of this waveform, we need standardization and quantification of the plethysmograph as it is presented to the clinician. I believe that the clinician has a vital role to play in the discovery and verification of new uses of the waveform. As was pointed out (7) the clinician attempting to solve clinical questions by innovative means is often faced with highly processed information from their monitoring devices. In their zeal to simplify the clinician's life, medical device manufacturers strive to present as "clean" a signal as possible, not wanting to distract the care provider with the "messy details." The downside of this approach is the potential over simplification of complex physiology. It must be remembered that what is viewed as an artifact from one prospective (i.e., respiratory variation of the PPG while determining heart rate) becomes signal in another (i.e., using the same respiratory variation of the PPG to predict fluid responsiveness).

In conclusion, I believe we need: 1) better equipment generating waveforms that can be quantified in a standardized manner, 2) well-designed prospective studies demonstrating that we are measuring clinically relevant information, and 3) outcome studies showing that this information will help the clinician provide better care for their patients.

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Automated Regulation of Inspired Oxygen in Preterm Infants: Oxygenation Stability and Clinician Workload

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Premature infants are at an increased risk of ophthalmic, neurologic, and respiratory sequelae related to inadequate maintenance of oxygenation and exposure to increased levels of inspired oxygen. Management of inspired oxygen is complicated in this population by an increased variability in oxygenation. Automated regulation of the fraction of inspired oxygen is a technology that has a potential of improving such outcomes as well as impacting personnel workload. This is a review of current experimental evidence on the effectiveness of automated regulation of inspired oxygen and its effects on oxygenation variability and personnel workload during the care of premature infants.

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Supplemental oxygen is given to otherwise hypoxemic premature infants to maintain adequate oxygenation and to avoid the deleterious effects of hypoxia. However, delivery of supplemental oxygen is not a risk-free therapy. Because of their premature birth, these infants are often exposed to oxygen at a time when their lungs, antioxidant system, and retina are too immature. Also, these infants often require supplemental oxygen for several days or weeks after birth. Therefore, they are at an increased risk for oxidative stress, lung injury, and retinopathy of prematurity (1–6). Management of the supplemental oxygen aims at minimizing exposure to increased levels of inspired oxygen while maintaining adequate oxygenation.

OXYGENATION VARIABILITY IN PREMATURE INFANTS

Under routine clinical conditions, management of the fraction of inspired oxygen (F_{IO_2}) is often complicated by fluctuations in oxygenation. These fluctuations vary in severity and frequency. Fluctuations associated with worsening or improvement of a respiratory condition occur gradually, and are relatively simple to correct while other fluctuations can occur quite frequently and are often characterized by rapid and severe changes in oxygenation (7–11).

Compared to other patient populations in intensive care, premature infants are at increased risk of developing complications related to fluctuations in oxygenation, which are believed to influence the development of retinopathy of prematurity (12–17). Intermittent hypoxemia can also have a negative impact on airways, lung vasculature, and other organs (18–21) while exposure to high concentrations of inspired oxygen can lead to development of permanent respiratory sequelae (1–4), which is associated with impaired neurologic outcome (22,23).

These fluctuations in oxygenation are detected by arterial oxygen saturation monitors (Spo_2) and trigger a personnel response. The response to the occurrence of hypoxemia usually consists of a transient increase in F_{IO_2} until normoxemia is restored. In the event of hyperoxemia, F_{IO_2} is gradually reduced. Under standard clinical conditions, personnel-to-patient ratio and increasing amounts of caregiver workload often do not permit full attention to these tasks. As a result, the response time when Spo_2 is outside an intended range of oxygenation is affected. Delayed responses can prolong exposure to unnecessarily high concentrations of supplemental oxygen or periods of hypoxemia.

Recent, multicenter data has shown that premature infants who require supplemental oxygen spend only about half of the time within individual center's intended range of oxygenation. Of the remaining time, about 20% is spent with Spo_2 readings below and about 30% above the intended range (24,25). Spo_2 readings in hyperoxemia in infants receiving supplemental oxygen could only be attained by providing unnecessarily high concentrations of inspired oxygen.

RATIONALE FOR AUTOMATED REGULATION INSPIRED OXYGEN

Automated regulation of the inspired oxygen in premature infants is intended to address the abovementioned issues by reducing periods of hyper- and hypoxemia, and limiting the exposure to high concentrations of inspired oxygen. The rationale that supports

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the development of automatic F_{IO_2} control is based on the timely F_{IO_2} adjustment to increase the alveolar oxygen concentration, followed by prompt weaning as soon as the additional oxygen is no longer needed.

These tasks could also be achieved with manual adjustments by clinical personnel. However, they can become time-consuming and increase workload.

EXPERIENCE WITH AUTOMATED F_{IO_2} REGULATION: OXYGENATION STABILITY AND WORKLOAD

Various studies have shown the feasibility of automated F_{IO_2} regulation for the care of premature infants. Moreover, automated F_{IO_2} regulation shows improvement in oxygenation stability around intended ranges of oxygenation compared to routine care and even when compared to nursing care dedicated to oxygen regulation (26–32).

When assessing the comparisons between automated and manual F_{IO_2} regulation in regard to oxygenation stability and frequency of manual interventions, it is important to consider the basal rate of variability of the studied population and personnel responsiveness. Comparisons of automated F_{IO_2} regulation to manual interventions are not likely to benefit infants who present with minimal or no variability in oxygenation. On the other hand, comparing automated F_{IO_2} regulation to routine care that is relatively unresponsive to fluctuations in oxygenation is likely to show greater benefits in comparison to more dedicated or attentive care. Also, depending on predetermined objectives for the automated system, not all such systems may be designed to address the different forms of oxygenation variability.

Clinically, the most important goal of automated F_{IO_2} regulation is to stabilize oxygenation. Automated F_{IO_2} regulation prolonged the time within an intended range of oxygenation compared to routine care consisting of adjustments at two hourly intervals (26,27,29) or manual adjustments every 20–30 min, even when compared to a more dedicated care with adjustments every 2–3 min (28). Moreover, automated F_{IO_2} prolonged the time within an intended range of oxygenation even when compared to fully dedicated care (29,32). These data illustrate the efficacy of this type of automation.

Infants with very frequent and/or acute fluctuations in oxygenation increase the demand for personnel time and also are a greater challenge for automated F_{IO_2} regulation. Not all systems described in the literature have been developed to address these fluctuations. In some of these, the response of the automated system consists of a user alert (26) or, in others require manual intervention because of inadequate system response (27,30). An automated F_{IO_2} controller designed to assist during acute episodes of hypoxemia increased the time within an intended range in comparison to the time spent by a fully dedicated nurse at bedside in a group of preterm infants who presented with an average of 15 episodes of hypoxemia per hour (32).

Under these challenging conditions, quantification of the effort required for tight control showed that the nurse adjusted F_{IO_2} a mean of 29 times an hour. This frequency does not fully indicate workload since continuous dedicated attention is needed at the onset, throughout, and at the end of the episode of hypoxemia. Reducing the workload resulting from these repetitive tasks may lead to a more effective use of personnel.

ASSESSING OXYGENATION

Perhaps, the most important component in the routine or automated process of F_{IO_2} regulation is continuous assessment of oxygenation. This can be done using indwelling Pa_{O_2} electrodes inserted through an umbilical artery catheter, transcutaneous PO_2 electrodes ($tcPO_2$) or arterial oxygen hemoglobin saturation measurements by pulse oximetry (Sp_{O_2}). Indwelling measurements are limited by availability of an invasive line. $tcPo_2$ is noninvasive, but depends on electrode temperature for accuracy. The continuity of $tcPo_2$ measurements is therefore affected by changes in application site to avoid thermal injury. Sp_{O_2} provides a continuous noninvasive assessment of oxygenation. Sp_{O_2} setup is relatively simple and is widely used in newborn intensive care units.

PULSE OXIMETRY TO DETECT HYPEROXEMIA AND HYPOXEMIA

Interpretation of Sp_{O_2} to detect and respond to hypo- or hyperoxemia is done in the context of the relationship between Sp_{O_2} and Pa_{O_2}, as depicted by the sigmoid-shaped O_2 dissociation curve. In the range of hyperoxemia, relatively small changes in Sp_{O_2} are associated with large changes in Pa_{O_2}. Data (33) show that a threshold Sp_{O_2} around 94% and 96% would correctly classify as hyperoxemic most Pa_{O_2} readings above 80 or 90 mm Hg. Most false-positive readings would be in the high–normal range (>60 mm Hg) and none in the low (<40 mm Hg) or low–normal Pa_{O_2} range (40–60 mm Hg). Therefore, a gradual reduction in F_{IO_2} in response to high Sp_{O_2} will correct most hyperoxemic events and is unlikely to lead to hypoxemia.

In the range of hypoxemia, most readings below a Sp_{O_2} threshold around 85% and 88% are associated with Pa_{O_2} readings in hypoxemia (<40 mm Hg), a small fraction with readings in the low–normal range (40–60 mm Hg) and none in the high Pa_{O_2} range (>80 mm Hg). Therefore, a F_{IO_2} increase in response to hypoxemia detected by Sp_{O_2} will be appropriate in most instances and unlikely to result in hyperoxemia.

ARTIFACT OR TRUE HYPOXEMIA?

The reliability of Sp_{O_2} in premature infants is especially sensitive to motion because of the relatively

low pulse pressure. Motion can produce venous blood pulsation and/or disrupt the optical pathway from the transmitter to receiver side of the probe. Despite documented improvements in Spo_2 technology, some hypoxemic episodes detected by pulse oximetry are considered artifactual. Visual inspection of the infant may reveal significant movement of extremities, absence of conclusive signs of cyanosis, and a transient mismatch between oximeter pulse rate and heart rate monitors. However, these observations cannot exclude true hypoxemia. To the contrary, increased infant activity and changes in heart rate, lung volume, and ventilation have been associated with hypoxemia episodes (9,10). Moreover, hypoxemia is more prevalent during arousal and indeterminate sleep states compared to periods of active or quiet sleep (11).

The response to an episode of hypoxemia and simultaneous motion, either by an automated system or by a caregiver, involves the risk of unnecessary oxygen exposure when the episode is artifactual. While the value of avoiding exposure to unnecessary supplemental oxygen is unquestionable, failure to assist a true hypoxemic episode because suspicion of artifact may allow alveolar and tissue hypoxia to increase.

Accuracy of Spo_2 is influenced by intrinsic patient conditions, such as low perfusion or inadequate setup of the oximeter (34). These conditions, however, are particular not only to automated regulation of Fio_2 but also to routine care. It is ultimately the clinician who decides if the use of pulse oximetry is appropriate and sufficiently reliable to monitor an infant.

When used in infants with frequent episodes of hypoxemia, automated Fio_2 regulation during every episode resulted in negligible overshoot with $<3\%$ of hypoxemia episodes followed by readings in hyperoxemia (32). If most of these episodes of hypoxemia had been artifactual, the additional oxygen would have had a higher rate of overshoot.

SIGNAL DROP OUT: MISSING Spo_2 INFORMATION

Poor signal quality can lead to periods of missing Spo_2 information, as determined by the built-in oximeter validation algorithms. This leaves clinical personnel or an automatic system without feedback information. As mentioned above, hypoxemia can be associated with body movement; therefore, there is the possibility that a period of missing Spo_2 information caused movement is accompanied by undetected hypoxemia. On the other hand, if the missing Spo_2 period is caused by technical factors, it could result in a period of unnecessary oxygen exposure. This, however, may resolve as soon as the clinician responds to the appropriate alarms and warnings given by the pulse oximeter and/or the automatic system. Data obtained during clinical use of automated Fio_2 control indicated that most periods of missing Spo_2 data were followed by periods of hypoxemia (32).

AUTOMATED SYSTEM RESPONSE

The method of automated Fio_2 regulation should modulate its response to severity, duration, rate of change and direction of the fluctuation in oxygenation. Optimization of the timing between Spo_2 events and Fio_2 adjustments is important when the objective is to assist rapidly ensuing and frequent hypoxemia episodes, while requirements are less for assisting infants who present with mild or gradual changes in oxygenation. A long delay may result in prolongation of hypoxemia or exposure to higher concentration of inspired oxygen when it is no longer needed.

Spo_2 data are averaged over a running window to reduce the effect of short variations. A long averaging window can slow detection of changes in oxygenation, and can increase the inertia of automated control leading to overshoot. A shorter averaging window enables the automated system to determine its own response time based on the variables mentioned above.

The mode of delivery should be optimized to produce changes in the inspired gas with minimal delays in setting adjustments at the controller. Optimized gas mixing can be accomplished by increased circulating flow rates in the ventilator and minimizing reservoir spaces.

RISKS AND BENEFITS

Failure or suboptimal function of the measurement, delivery or control components of automated Fio_2 control may involve risks of exposure to hypoxemia or unnecessarily high concentrations of inspired oxygen. The use of this technology may result in only a relative increase of these risks, which may be, in part, present during routine care because with the exception of the manual regulation component, the measurement and delivery components are standard.

Monitoring and assistance during routine care may be sufficient for infants with mild or gradual fluctuations in oxygenation or those whose disease condition requires high Fio_2 continuously. On the other hand, infants who present with frequent and acute changes in oxygenation may obtain a greater benefit from automated assistance. Dedicated assistance to these infants imposes additional workload on personnel.

Automated Fio_2 regulation is aimed mainly at conducting repetitive and time consuming tasks. It is meant to be used in a manner in which the time dedicated by the caregiver to patient care is not affected by these tasks. However, automated Fio_2 regulation may in some instances result in an unwanted reduction in the time dedicated by the caregiver to patient monitoring. Since hypoxemia episodes in preterm infants have a wide etiology, automated

F_{IO_2} regulation could mask the effects of a triggering event such as hypoventilation. Proper and timely monitoring of cardiorespiratory variables should be assured to avert this type of situation. On the other hand, one could argue that an automated F_{IO_2} increase should at least reduce the detrimental effects until corrective actions are taken.

Assistance for every episode of hypoxemia with an increase in F_{IO_2} could result in additional exposure to oxygen. Timely weaning when hypoxemia resolves should limit the exposure to oxygen. As mentioned above, overshoot (hyperoxemia) was observed in <3% of hypoxemia episodes corrected with an automated F_{IO_2} increase. Nonetheless, compared to no intervention in the form of supplemental oxygen, the lungs would be exposed to higher concentrations of oxygen and therefore an increased risk of lung injury. A predetermined absence of intervention during hypoxemia episodes assumes that the effects of these episodes on the central nervous system and other organs are irrelevant to outcome.

SUMMARY

Supplemental oxygen administration, although a necessary and often life-saving therapy, has side effects that are of relevance in the premature infant population. This population has a high risk for respiratory, neurologic, and ophthalmic compromise. Therefore, there is a need for gentler, yet effective, oxygenation support.

The emergent availability of improved technology for oxygenation monitoring and computing has facilitated the development of automated modes of regulation of supplemental oxygen for the preterm infant. Although this technology has been only used experimentally, preliminary results suggest future impact on patient care and practice. This, however, remains to be tested. Future research will determine the role of this strategy in improving pulmonary, ophthalmic, and neurological outcome in premature infants, as well as in determining the true impact on caregiver workload.

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Chip-Scale Sensor System Integration for Portable Health Monitoring

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The revolution in integrated circuits over the past 50 yr has produced inexpensive computing and communications systems that are powerful and portable. The technologies for these integrated chip-scale sensing systems, which will be miniature, lightweight, and portable, are emerging with the integration of sensors with electronics, optical systems, micromachines, microfluidics, and the integration of chemical and biological materials (soft/wet material integration with traditional dry/hard semiconductor materials). Hence, we stand at a threshold for health monitoring technology that promises to provide wearable biochemical sensing systems that are comfortable, inauspicious, wireless, and battery-operated, yet that continuously monitor health status, and can transmit compressed data signals at regular intervals, or alarm conditions immediately.

In this paper, we explore recent results in chip-scale sensor integration technology for health monitoring. The development of inexpensive chip-scale biochemical optical sensors, such as microresonators, that are customizable for high sensitivity coupled with rapid prototyping will be discussed. Ground-breaking work in the integration of chip-scale optical systems to support these optical sensors will be highlighted, and the development of inexpensive Si complementary metal-oxide semiconductor circuitry (which makes up the vast majority of computational systems today) for signal processing and wireless communication with local receivers that lie directly on the chip-scale sensor head itself will be examined.

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Increasing the measurement and monitoring of critical physiological variables could have a tremendous effect upon health care from the hospital to the home setting for patients from infants to the elderly. For example, blood oxygenation is a critical physiological variable that indicates life, death, and disability. The ability to pervasively monitor oxygenation could have a profound effect in cardiac and pulmonary disease, asthma, and sudden infant death syndrome monitoring and diagnosis, and in elderly home care. In 1999, 720,000 deaths in the United States were directly related to cardiac disease, fully 30% of all deaths in the United States that year, with the majority (462,000 or 64%) due to sudden cardiac death (1). Congestive heart failure affects more than 3 million people in the United States, costing more than $10 billion in treatment annually (2). Chronic obstructive pulmonary disease affects an estimated 10 million adults in the United States, and costs approximately $32 billion annually (3). The thread that binds all of these diseases and syndromes together is that they all hinge on the failure of the cardiopulmonary system to effectively exchange gases and deliver oxygen to vital organs. All of these diseases can be monitored in at-risk patients, from the hospital to the home, using a pulse oximeter. Next generation pulse oxygenation systems may be so small, comfortable, and inexpensive that they may be worn pervasively and continuously to monitor for alarm conditions and for disease progression. These data could be transmitted without user intervention to a wireless station (cell phone, computer), and could be monitored by a central alarm alert center. Innovations such as these could have a transformative effect on at-risk populations and the elderly, producing critical early response warnings, improving health-care delivery through a quantitative disease progression database, and enabling the elderly to remain at home, improving quality of life, and saving health care funds in an ageing population. This is one example of the impact that applying state-of-the-art semiconductor and optical technology to the miniaturization and portability of sensing systems could have on revolutionizing health care.

Home monitoring is an emerging area of health care that will significantly affect the quality of life of ageing populations through the potential delay of entry into health care facilities. The elderly population

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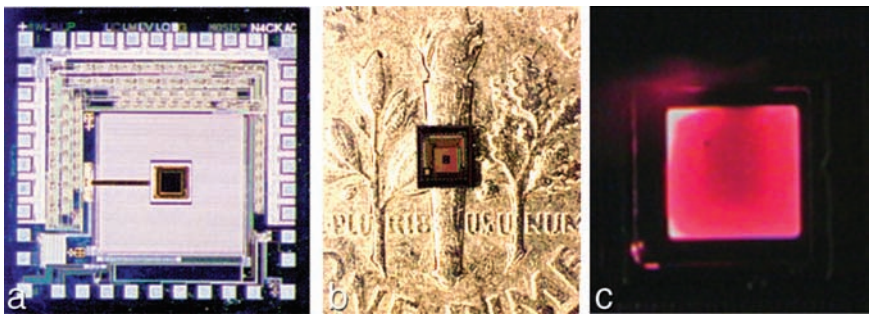

Figure 1. Photomicrographs of integrated LED/Si PD/Si CMOS circuit microsystem: (a: left) near infrared light emitting diode in the center of Si PD array with integrated Si CMOS analog and digital signal processing circuitry; (b: center) integrated chip from (a) on the back of a dime (shows size); (c: right) Red light emitting diode integrated onto the same Si CMOS chip, emitting under power.

of the United States and the entire world continues to grow at ever increasing rates. By 2025, the world population of individuals older than 65 yr is expected to be more than 800 million (4). By the year 2050, approximately 20% of the world's population will be 65 yr or older, upwards of 2.5 billion individuals (5). The US population older than 65 yr is now around 35 million, and is expected to reach 55 million by 2020, and 80 million by 2040, comprising more than 20% of the total population (6). Although currently 13% of the total US population, the elderly consume one-third of health care spending and one-half of all physician time (7). In 2003, total health care expenditures were $1.7 trillion, more than 15% of the US gross domestic product (8). This amounts to more than $500 billion spent on health care for the elderly in 1 yr. Miniaturized, portable, integrated monitoring systems, again, may have a tremendous impact upon the availability and cost of such home health monitoring systems.

Health monitoring systems can be grossly partitioned into the functional subgroups that include the sensor, the signal processing, and the communications units. The identification and integration of appropriate, inexpensive sensors, the low power, compact signal processing that will enable portability, and a low power communication approach are all critical to the realization of chip-scale health monitoring systems. Sensing technology is under intense research investigation, and many types of sensors have been reported. However, many of these sensors are bulky, insensitive, and consume a great deal of power. Optical sensors, which are among the most sensitive and can be miniaturized, will be the focus of this paper. For health monitoring, we will discuss two types of optical sensors: noninvasive optical sensors, such as pulse oximeters, and fluidic sensors, such as microresonators, that use one to a few drops of human fluid input. This is a subset of optical monitoring systems; miniaturization and integration will also strongly impact the next generation of imaging and optical probe (fluorescence, Raman, etc.) technologies as well by significantly increasing portability and reducing power consumption. The goals of both areas of research are to leverage current engineering technology breakthroughs in semiconductors and in integration to create miniaturized, portable, inexpensive sensor systems for health monitoring.

NONINVASIVE OPTICAL MONITORING MICROSYSTEMS

Pulse oximeters measure arterial blood oxygenation, which are critical physiological data, since insufficient oxygen can quickly lead to irreversible brain and vital organ damage. Pulse oximetry is currently the standard of care for noninvasive arterial oxygen monitoring. Most current pulse oximeters are bulky, limit user mobility due to wires, have limited accuracy ranges, and have limited sensor sites that are often poorly perfused. The next generation of miniaturized, integrated pulse oximetry systems may be more accurate, wearable, wireless, and offer more sensor site options. In the future, there may be pulse oximetry systems that have optics, signal processing, wireless communication, and a battery, all integrated onto a sensor head that continuously monitors blood oxygenation, with alarms and data that are wirelessly transmitted.

By leveraging inexpensive micro- and nanotechnologies, it will be possible to create an accurate oxygenation monitoring system with wireless communication integrated into an unobtrusive, wearable package. Critical technical aspects of next generation pulse oximeters include the integration of low power, geometrically optimized optical emitters and photodetectors, dedicated low noise, low power signal processing, and wireless communication implemented in inexpensive Si complementary metal-oxide semiconductor (CMOS), and packaging that will enable continuous wear. By integrating the signal processing with the communication, the oxygenation can be calculated directly on the signal head, enabling data compression and intermittent transmission for data within the safe monitoring range, with the option for immediate alarm transmission if the data are outside of the acceptable range.

The integration of multiple light emitting diodes (LEDs) with geometrically optimized photodetectors may enable pulse oximeters that are smaller and use less power through improved collection efficiency. Figure 1 is a photomicrograph of an integrated optical emitter/photodetector pair that has been implemented in Si CMOS that constitutes first step in this direction. Figure 1a is a close-up of the integrated optoelectronic system, in which a thin film (1-μm-thick) AlGaAs/GaAs/AlGaAs LED (that emits in the near infrared) has been integrated into the center of a

Si CMOS photodetector array (9). Analog emitter driver and photodetector receiver circuitry are implemented on the chip in Si CMOS, and the digital circuitry on the integrated circuit provides the signal processing capability. Figure 1b is a photomicrograph of the integrated circuit shown in Figure 1a on the back of an American coin (dime) to show the size of the integrated system. Figure 1c shows the LED (integrated onto the same chip shown in Fig. 1a) emitting in the red wavelength region, under power. The Si CMOS integrated circuit was fabricated through the MOSIS foundry, and is a standard Si CMOS integrated circuit. The advantage of using foundry Si CMOS is that the photodetector array geometrical format can be arbitrarily defined (which can be optimized for pulse oximetry applications, which Fig. 1 is not), and that the interconnections between the analog photodetector output signal and the receiver circuitry are short, and thus less prone to noise pick-up. Analog and digital signal processing for noise reduction (and signal to noise improvement) can be implemented on the chip, which is on the sensor head, and wireless communication has previously been implemented in Si CMOS.

Integrated chip-scale sensor systems that integrate multiple types of function are newly emerging technologies. Mixed signal microsystems have traditionally integrated analog and digital electronics onto the same chip ("System on a Chip") or into a single package ("System in a Package"). New, "ultra" mixed signal systems may integrate optics/photonics, microfluidics, micro-electromechanical structures, and/or radio frequency (wireless) capabilities into the system, as well. It is this type of integration that enables sensors, such as electrical sensors or optical sensors, to be integrated or packaged with chip-scale control and signal processing electronics and communication (e.g., wireless) functions. One emerging technology that enables these ultramixed signal integrated systems is the heterogeneous integration of compound semiconductor devices (for optical and wireless functions) with foundry Si CMOS analog and digital circuitry.

OPTICAL MONITORING MICROSYSTEMS USING HUMAN FLUIDS

More invasive sensing, such as technologies that use human fluids as sensor inputs, offers biological and chemical sensing opportunities that are often not available in a noninvasive probe format. Chip-scale sensors have been demonstrated using a variety of sensing mechanisms, including electrochemical, thermal, optical, and mass-sensitive transducers. Optical sensors are characterized by their versatility, sensitivity, and potential for miniaturization (10–13). The discrimination of sensed analytes using optical index of refraction changes are commonly used in laboratory instruments such as surface plasmon resonance sensing systems. However, miniaturized optical sensors with high sensitivity are just emerging. Optical sensors such as high-quality microresonators are attractive candidates for realizing customizable sensing in a miniaturized format.

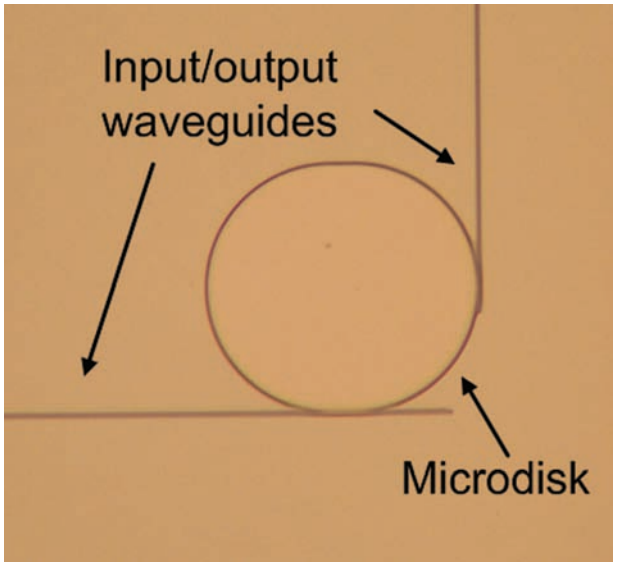

Figure 2. Photomicrograph of a 100-μm diameter polymer microdisk glucose sensor.

Microresonators, which include microrings and microdisks, are attractive optical sensors, since they have a large quality factor (Q factor) and compact size (14,15). These devices are becoming widely published for use as lasers (16) and filters (17), and have been demonstrated in typical inexpensive materials for chip-scale sensors: silica (18), polymers (19), and III–V compound semiconductor materials (20). These resonators are highly sensitive to optical index of refraction changes in the surrounding environment, and reports using these resonators for sensors as gyros (18), for pressure sensing (21), fluor signal concentration sensing (22), and as distributed Bragg reflectors (23) are emerging. Several researchers have reported microcavity sensors in various formats including mirroring, microdisk, and modified mirrors (14,24,25). Polymer microcavity sensors with surface modification and microcavities measuring glucose concentration in aqueous solutions (25) have been reported, and enhancement of a fluorescence signal was demonstrated using an integrated optical microcavity (26). Essentially, microresonator sensors sense index of refraction changes on the surface of the sensor, which causes a change in the resonator to waveguide coupling. These sensors are typically 20–200 μm in diameter in dinner plate (disk) or ring shapes that are about 1–3-μm-thick.

The microdisk sensor shown in Figure 2 is an orthogonal microresonator, since the input and output coupling regions are orthogonal (27). This microdisk consists of three parts: the input waveguide/coupling section, microdisk cavity (sensor portion), and output waveguide/coupling section. Part of the input beam is coupled into the microdisk by the input coupling

section. This coupled optical signal is trapped in the microdisk at the wavelengths of resonance, and circulates in the disk section. Optical resonance occurs when the circulating beam satisfies the cavity resonant condition: the total phase shift per roundtrip of the optical beam in the resonator is equal to an integer multiple of $2[\pi]$. The output beam is at a maximum when the resonance condition is met for any particular wavelength. If the optical structure (refractive index) of the microdisk or of the surface above the microdisk is changed (for example, through a surface chemical or biological binding/hybridization sensing event), the resonance condition will be altered, thus changing the output power. By monitoring the output power variation in the output waveguide (for example, with an integrated photodetector), orthogonal microresonators can be used as optical sensors.

There are several practical issues involved in the design and implementation of microresonator sensors. First, as shown in Figure 2, the input waveguide and output waveguide of the microresonator sensors should be perpendicular. This reduces undesired coupling of the input beam into the output waveguide or external collection system (e.g., photodetector or optical fiber), which can occur if the input and output waveguides are parallel to one another. The orthogonal approach also eliminates additional bent output waveguides for exciting and collecting the optical beam into the cavity, so the total size of the sensor system, which includes the input/output waveguides, can be significantly reduced in comparison to sensors with nonorthogonal configurations. Second, the manufacturability of the microresonator sensor is important, since this dictates cost. Also, the ability to format arrays of microresonator sensors on a single substrate is important if discrimination through overlapping signatures is desired. If there are multiple microresonator sensors, each with a different surface customization, then the different sensor outputs, with different signatures for a single sample, can be signal-processed to more precisely determine the sample content.

Both the manufacturability and the ease of fabricating arrays of microresonators lead to vertically coupled microresonators (VCMRs). The distance between the input waveguide and the microresonator and between the output waveguide and the microresonator determines the coupling, and is typically submicron in distance. Lateral separation between these waveguides and the microresonators that are this small do not use typical, inexpensive, high-throughput photolithography tools but, rather, more expensive, lower throughput electron beam lithography. In contrast, if the input/output waveguides are stacked above or below the microresonator with a submicron spacer layer in between, then a VCMR is created, and standard photolithography can be used

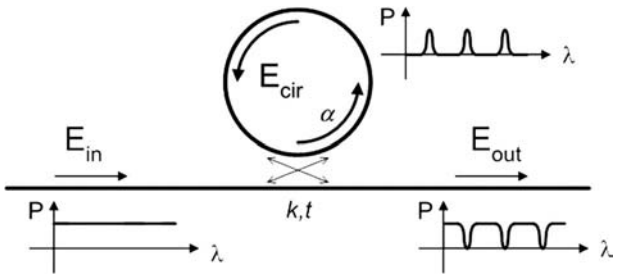

Figure 3. Input (E_{in}) and output (E_{out}) of a microresonator sensor with a single input/output waveguide. The circulating power in the resonator is also shown in the upper right.

to fabricate inexpensive microresonators in array format. Using VCMRs, inexpensive, standard microelectronics fabrication can be used to fabricate the sensor arrays, thus leveraging the microelectronics industry for integrated optical sensing systems.

To integrate microresonator sensors into a self-contained chip-scale microsystem, the inputs and outputs of the microresonator must be well understood. The microresonator input is a single-mode laser input. The output power of the microdisk sensor is oscillatory as a function of wavelength (spectral output), and reaches maximum values when the resonance condition is satisfied (for multiple wavelengths). As the refractive index of the microresonator surface changes, the resonant condition changes, and the peak wavelengths shift. At any particular monitored wavelength, there is a change in output power (either increasing or decreasing, depending upon where the monitored wavelength lies on the oscillatory spectrum). Figure 3 shows the input and output of a linear (not orthogonal) microresonator sensor. Since microresonators are highly sensitive to index of refraction changes at the surface of the sensor, surface customization can be used to sensitize the sensor surface. Thus, DNA hybridization and antibody–antigen binding can be sensed on the microresonator surface for biological sensing, and chemically selective membranes can be used for selective chemical detection. The microdisk resonator shown in Figure 2 was implemented in polymer material on a Si substrate and demonstrated in operation as a glucose sensor.

Optical sensors are attractive due to their high sensitivity and miniature size; however, the integration of chip-scale optical sensing systems dictates the implementation of an optical source, sensor, and photodetector. In the case of microresonator structures, waveguides (which confine the light) act as input/output to the sensor, and so a planar lightwave integrated circuit that combines both active and passive optical elements at the chip scale is an ideal, and emerging viable technical, solution. To realize this integration, the waveguide and passive devices are deposited or spin coated using traditional chemical vapor deposition (nitrides, dioxides) or spin coating (polymers) techniques. The active devices are thin film optoelectronic devices, in which the substrate has been

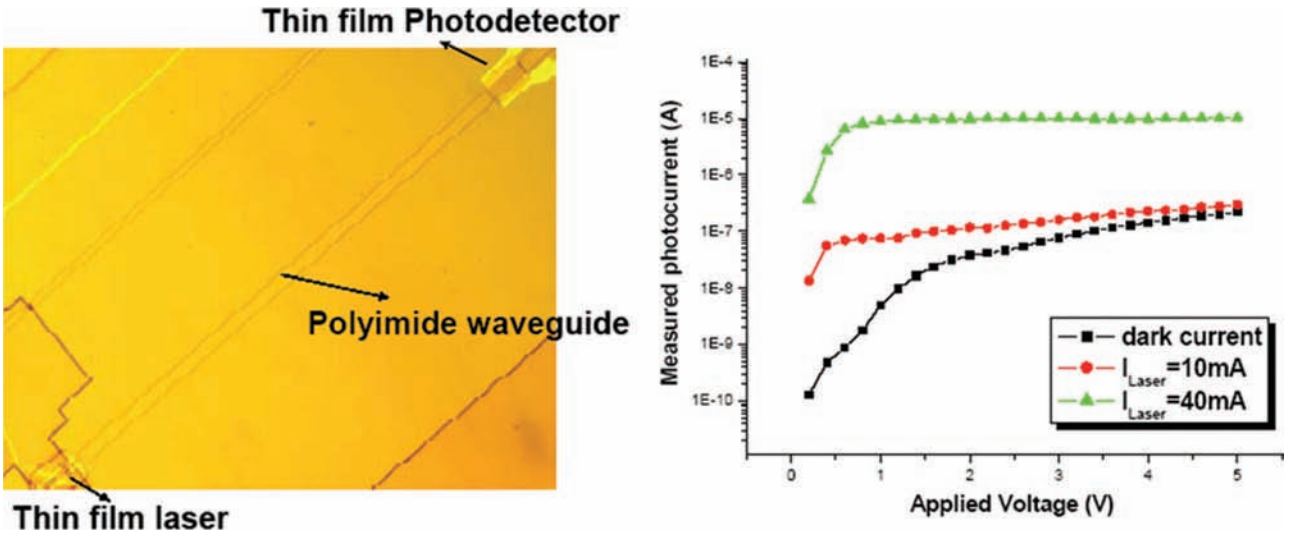

Figure 4. Photomicrograph and measured data from thin film edge emitting laser, polymer waveguide, and thin film photodetector all integrated onto a SiO_2/Si substrate.

removed, thus resulting in devices on the order of 1–5-μm-thick, which are ideal for chip-scale planar lightwave integrated circuit integration. The entire structure can also be designed for encapsulation, with only the sensor exposed to the sensed analyte.

The integration of thin film active optoelectronic devices (emitters, photodetectors) onto Si, Si CMOS (28), and FR-4 (29) substrates have been demonstrated using spin-coat planarization, thin film device bonding (also called heterogeneous integration), and spin coat/photolithographically defined passive waveguide structures. Thin film devices embedded in polymer waveguides on silicon (30), ceramic (31), and FR-4 (32) substrates have also been demonstrated. For example, thin film InGaAsP-based edge emitting laser, polymer waveguide, and independently optimized thin film InGaAs photodetector were all co-integrated onto a SiO_2/Si substrate (33). Figure 4 illustrates that more than one thin film compound semiconductor device can be integrated onto a single chip-scale Si substrate. Figure 4 (left) is a photomicrograph of an integrated laser/waveguide/photodetector chip-scale system (approximately 4 mm $\times$ 1 mm) and the resultant data from that system (34). This integrated planar optical system consists of a thin film edge emitting laser, a polymer waveguide, and a thin film waveguide photodetector. The data to the right of Figure 4 show the output of the photodetector under three laser output conditions. These data show the photodetector dark current (when the laser is off), and the photodetector current when the laser is biased below threshold (very little light output from the laser) and above threshold (high light output from the laser). As expected, the photodetector current output tracks the laser operation, demonstrating that the laser and photodetector are optically connected by the waveguide. This system is a significant step toward chip-scale integrated optical sensing systems; to realize an optical sensing system, an optical sensor can be inserted into the waveguide section of this integrated substrate. The laser will act as the sensor optical source, and the photodetector can monitor the output of the sensor. Currently, our group is integrating a microresonator sensor into this system toward a complete chip-scale optical sensor system.

This integration means that highly sensitive optical sensing systems, previously addressed by external lasers and optics, can now be fully portable, and that many waveguide-based systems (sensor and other) that currently use an external laser will now be able to use an on-chip laser, freeing the system from the wall power plug and significantly enhancing system portability. In addition to the laser/waveguide/detector integrated chip-scale system and numerous waveguide/detector and optoelectronic device/Si CMOS circuit integrated systems, a polymer microring has been integrated with a thin film InGaAs photodetector, another step toward chip-scale optical sensing systems, as shown in the photomicrograph in Figure 5 (35). In this research, a thin film active photodetector was embedded in the output waveguide of the microresonator, as shown in Figure 5, to provide optical to electrical for the output, replacing external photodetectors with integrated photodetectors, thus eliminating external coupling from the waveguide to an external fiber, which creates optical loss in the system. As discussed, this photodetector monitors the output of the waveguide, which changes in optical intensity (per the oscillatory spectrum) when sensing occurs on the microresonator surface.

CONCLUSIONS

Next generation miniaturized, portable, inexpensive integrated sensing systems will have a profound effect on health monitoring. Technologies for fabricating and integrating sensors into chip-scale portable systems stand at a threshold that promises to provide

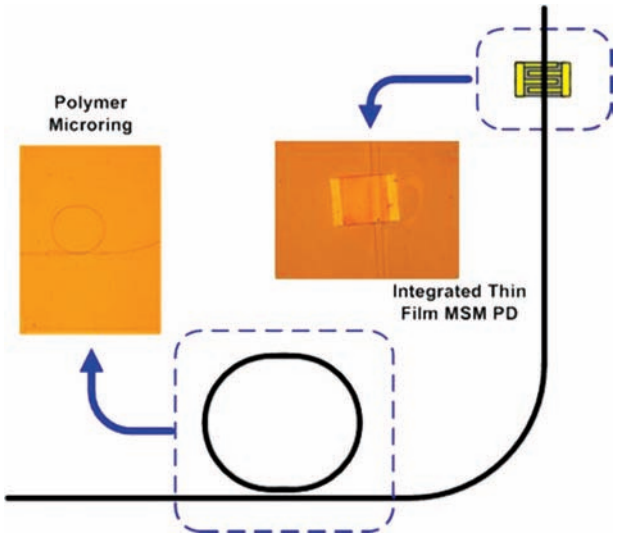

Figure 5. Planar polymer microring integrated with an thin film InGaAs photodetector embedded in the polymer output waveguide of the microresonator. The entire system has been on fabricated on a SiO_2/Si substrate.

wearable biochemical sensing systems that are comfortable, inauspicious, wireless, and battery-operated, yet that continuously monitor health status, and that can transmit compressed data signals at regular intervals, or alarm conditions immediately.

Recent research into chip-scale sensor integration for health monitoring includes the demonstration of small optical sensors, as well as the integration of the associated optical input and output necessary to drive these systems. Leveraging inexpensive Si CMOS circuitry fabrication technology and the circuitry itself for signal processing and wireless communication is key to the realization of inexpensive systems that have a high level of signal capture and signal processing capability for portable, miniature health monitoring systems.

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The Design, Use, and Results of Transcutaneous Carbon Dioxide Analysis: Current and Future Directions

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Transcutaneous carbon dioxide (CO_2) analysis was introduced in the early 1980s using locally heated electrochemical sensors that were applied to the skin surface. This methodology provides a continuous noninvasive estimation of the arterial CO_2 value and can be used for assessing adequacy of ventilation. The technique is now established and used routinely in clinical practice. Transcutaneous partial pressure of CO_2 ($tcPco_2$) sensors are available as a single Pco_2 sensor, as a combined Pco_2/Po_2 sensor, and more recently, as a combined Pco_2/Spo_2 sensor. CO_2 is still measured potentiometrically by determining the pH of an electrolyte layer. The methodology has been continuously developed during the last 20 yr, making the $tcPco_2$ systems easier and more reliable for use in clinical practice: smaller sensor size (diameter 15 mm, height 8 mm), less frequent sensor re-membraning (every 2 wk) and calibration (twice a day), sensor ready to use when connected to the monitor, lower sensor temperature (42°C or less), shorter arterialization time (3 min), and increased measurement reliability through protection of the membrane. The present $tcPco_2$ sensors still need to be regularly re-membraned and calibrated. One way to overcome these procedures is to use optical-only detection means. Two techniques have been developed using optical absorption in the near-infrared light, in the evanescent wave of a waveguide integrated in the sensor surface, or in a micro-optics sampling cell. Preliminary *in vitro* and *in vivo* CO_2 measurements have been performed. The sensor is not affected by drift over several days, and its response time is <1 min.

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The measurement of blood gas oxygen and carbon dioxide (CO_2) is an integral aspect of monitoring the respiratory status of a patient. The "gold standard" used to access these parameters is the analysis of arterial blood samples. The fact that arterial blood gas values may change rapidly in many clinical situations has stimulated the interest for a continuous measurement of these parameters. For monitoring the partial pressure of CO_2 (Pco_2), several methods have been described during the last three decades. Continuous intraarterial Pco_2 monitoring has been proposed since the 1970s. In this case, Pco_2 is either measured intraarterially using a miniaturized electrochemical or optical sensor, or fed into a gas chromatographic or a mass spectrometric detection system using a carrier gas or a vacuum (1–5). These techniques are not widely used clinically, mainly because of technical reasons: invasivity, size of the catheter, instability of the calibration due to clotting, or lack of reusability (6,7). It also is relatively expensive. End-tidal CO_2 measurement provides a noninvasive estimate of the arterial Pco_2 ($Paco_2$). It is routinely used in operating rooms, but it suffers limitations in patients with respiratory disorders and in nonintubated patients. Transcutaneous Pco_2 ($tcPco_2$) devices provide another option for the continuous noninvasive estimation of $Paco_2$, and in several situations is preferred to end-tidal CO_2 analysis (8–10). The purpose of this article is to review the current and future directions of $tcPco_2$ analysis.

A REVIEW

The measurement of Pco_2 on human skin surfaces was first described in 1960 by Severinghaus (11). Using a specially designed temperature-stabilized tissue Pco_2 electrode, he measured Pco_2 values of over 130 mm Hg on slightly blanched skin. Johns et al. (12), who attached an unheated Pco_2 electrode on skin from which part of the stratum corneum was stripped off, reported systematic studies in this direction in 1969. They were able to show that there is a linear relationship between skin surface Pco_2 and $Paco_2$ in the range from 20 to 74 mm Hg. A few years later, heated Po_2 sensors were described by Eberhard et al.[1] and by

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[1]Eberhard P, Mindt W, Hammacher K. Perkutane Messung des Sauerstoffpartialdrucks: Methodik und Anwendungen. Medizin-Technik 1972:26 (Tagungsausschuss Medizin-Technik, Stuttgart, 1972).

Huch et al.[2] These sensors measure the oxygen partial pressure at the surface of the skin and gave a close estimate of the arterial Po_2. The use of local heating through the sensor was the breakthrough allowing the continuous measurement of blood gases for prolonged time periods. This method was patented in 1971 (13). The initial goal was the measurement of oxygen in newborns to avoid the deleterious effects of both hypo- and hyperoxygenation (14). Several designs of this type of sensor have been described (15,16), and more than 10 companies have introduced them in the market. The methodology was later applied to the measurement of CO_2 (17). The first commercially available $tcPco_2$ sensors were introduced in 1980, and the combined $tcPo_2$–Pco_2 sensors in 1985. They have been continuously improved but are still using the same methodology to arterialize the cutaneous tissue. Initially, and correctly, the word "cutaneous" was introduced to describe the technique consisting of analyzing the concentration of the gas diffusing through the cutaneous tissue at the skin surface. "Cutaneous" is still used in the United States standards to describe blood gas measurements by skin surface sensors (18). However, most of the numerous publications describing the application of this technology in clinical routine have been using the word "transcutaneous," which is now the term most commonly used. European standards also use the word "transcutaneous" (19). The commercially available $tcPco_2$ sensors are electrochemical in nature. Other measurement techniques such as mass spectrometry and gas chromatography have also been proposed for the transcutaneous determination of blood gases, but have not been further developed (20,21).

METHODOLOGY

Transcutaneous measurement of Pco_2 makes use of the fact that CO_2 gas diffuses through body tissue and skin and can be detected by a sensor at the skin surface. By warming the sensor, a local hyperemia is induced, which increases the supply of arterial blood to the dermal capillary bed below the sensor. In general, this value correlates well with the corresponding $Paco_2$ value. Because of the elevated temperature of the sensor, the $tcPco_2$ is higher than the arterial value, and it has become a common practice to apply a correction to the transcutaneous value to provide a reading that corresponds as close as possible to $Paco_2$, the gold standard. The shift of $tcPco_2$ towards higher values is attributed to two main factors. First, the elevated temperature increases local blood and tissue Pco_2 by approximately 4.5%/°C (anaerobic factor). Second, the living epidermal cells produce CO_2, which contributes to the capillary CO_2 level by a constant amount (metabolic constant). The skin metabolism increases the $tcPco_2$ by approximately 5 mm Hg. The theoretical basis of the correction algorithm used by the manufacturers of $tcPco_2$ systems has been specifically described by Severinghaus (22).

In the case of oxygen determination by skin surface sensor, a sensor temperature of approximately 44°C is needed to obtain a significant correlation with the arterial value. At this temperature, especially in the premature infant, it is necessary to reposition the sensor every few hours. In the case of CO_2, a lower temperature can be applied, usually 42°C (23–26). Even at a sensor temperature of 37°C, a good correlation with $Paco_2$ has been reported (27), but the dynamic behavior of the $tcPco_2$ is influenced by the sensor temperature. At a high sensor temperature, the reactivity to fast Pco_2 fluctuations is considerably shortened (28). At a lower temperature, the application of heat creates an initial over-shooting of the $tcPco_2$ (29).

In the presently used transcutaneous electrochemical sensors, CO_2 is measured potentiometrically by determining the pH of an electrolyte layer separated from the skin by a highly permeable membrane, according to the method described by Stow and Randall (30) and Severinghaus and Bradley (31). A change of the pH is proportional to the logarithm of Pco_2 change. The pH is determined by measuring the potential between a miniaturized pH glass electrode and an Ag/AgCl reference electrode (17).

CURRENT AND FUTURE DIRECTIONS

$tcPco_2$ sensors are available as a single Pco_2 sensor, as a combined Po_2/Pco_2 sensor, mainly used in neonatology and, more recently, as a combined Spo_2/Pco_2 sensor for use in adults and infants (32) (Figs. 1 and 2).

The typical characteristics of a $tcPco_2$ sensor are listed in Table 1.

The sensor must be re-membraned every 1–2 wk, an easy straightforward procedure. The sensor must also be regularly calibrated. This implies that the monitor includes a calibration module and a gas cylinder. The monitor can automatically perform these calibration procedures. The sensor can then always be ready to use, eliminating the waiting time before use.

Today, $tcPco_2$ monitors are mainly used to estimate $Paco_2$ and/or to follow the trend of $Paco_2$ in a patient. It has found an application mostly parallel to the determination of oxygen through $tcPo_2$ or Spo_2 in various fields of medicine, such as neonatal intensive care (33), adult critical care (34,35), mechanical ventilation (36,37), anesthesia (38,39), bronchoscopy,[3] sleep

[2]Huch A, Huch R, Meinzer K, Lübbers DW. Eine schnelle, beheizte Pt-Oberflächenelektrode zur kontinuierlichen Überwachung des Po_2 beim Menschen; Elektrodenaufbau und –eingeschaften. Medizin-Technik 1972:26 (Tagungsausschuss Medizin-Technik, Stuttgart, 1972).

[3]Männle C, Herth FJ, Becker HD, Wiedemann K. Controlling of High Frequency Jet Ventilation (HFJV) by measurement of the transcutaneous carbon dioxide tension ($TcCO_2$) during rigid bronchoscopy. Chest 2003;124:125S (abstract).

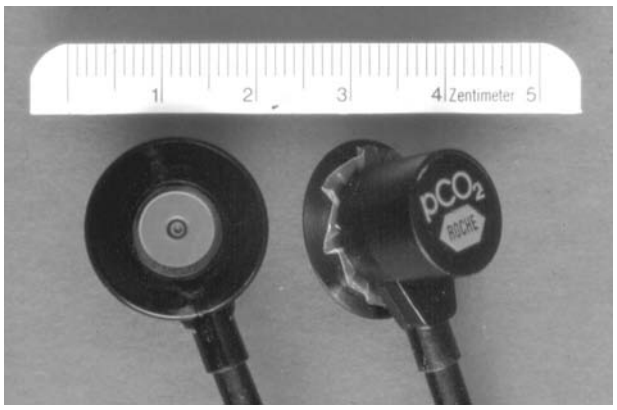

Figure 1. A $tcPco_2$ sensor in 1980.

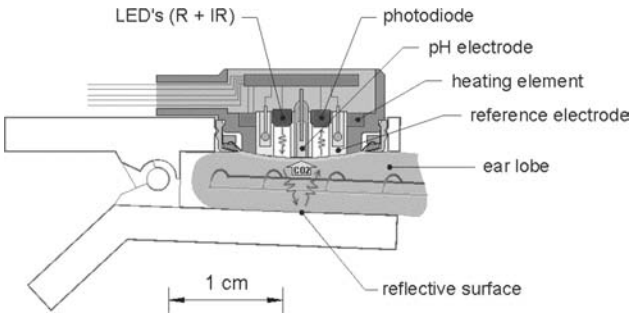

Figure 2. A combined Spo_2/$tcPco_2$ sensor at the ear lobe today.

Table 1. Typical Characteristics of a Transcutaneous Pco_2 ($tcPco_2$) Sensor

Size	
Diameter	15 mm
Height	8 mm
Weight	3 g
Pco_2 range	1–200 mm Hg (0.1–27 kPa)
In vitro response time (10%–90%)	50 s
In vitro drift	≤0.5%/h
Arterialization time after application of the sensor on the skin	3–10 min, depending on the site

studies and apnea testing (40,41), pulmonary stress testing, and respiratory research. It is of particular value in following the immediate effect of any therapeutic measure, which has a direct or indirect influence on the patient's ventilatory efficiency. When used to estimate $Paco_2$, the transcutaneous methodology is limited in some clinical situations, e.g., during profound peripheral vasoconstriction and circulatory centralization or in the presence of skin edema.

The most recent developments of $tcPco_2$ sensors have been oriented towards:

The combination with other parameters such as Spo_2 (32), e.g., in adults to overcome the limitation of $tcPO_2$ use for measuring the patient's oxygenation. The integration of Spo_2 in a heated sensor may also increase the reliability of the Spo_2 measurement in cases of low perfusion and the sensitivity to oxygen saturation change (40,42).

Use of lower sensor temperature, e.g., 42°C or lower, to avoid the frequent repositioning of the sensor.

Diminution of the size of the sensor, especially for application with premature infants and on specific peripheral sites such as earlobe, toe, etc. The measurement at the earlobe increases the sensitivity of the $tcPco_2$ sensor to CO_2 change (42).

Increasing the sensor's stability to decrease the need for recalibrating the sensor.

Increasing the function time between re-membraning.

Increasing the reliability of the measurement, e.g., by protecting the sensitive sensor surface to avoid any damage of the membrane during the functional period.

Digitalization of the signal inside the sensor[4].

And, in general, making the use of transcutaneous blood gas monitoring as easy as pulse oximetry.

A limitation of the presently used $tcPco_2$ methodology is related to the use of the electrochemical measurement technique, more specifically the need to periodically re-membrane and calibrate the sensor. One way to eliminate these procedures may be to apply an optical-only measurement principle as used in pulse oximetry and capnometry. A $tcPco_2$ sensor using an optical-only detection means was described by Salzmann et al. (43). CO_2 is determined by measuring its optical absorption in the evanescent wave of a waveguide integrated in the surface of the sensor. The surface sensing is combined with modulation spectroscopy providing high selectivity and sensitivity. The use of near-infrared light (1580 nm) allows the use of reliable and cost-effective devices such as standard telecommunication fibers and laser. The high selectivity is obtained by tuning the narrow spectral-width of the laser source on the specific absorption line of the molecule to be detected (Fig. 3). Alternatively, CO_2 has been measured in a micro-optics-type miniaturized sampling cell. The sample volume, adjacent to the skin surface, is reduced to approximately 1 mm^3 allowing a response time of <1 min. The optical sensor can be precalibrated in the factory and is not affected by drift over several days. This technique may offer an alternative to the electrochemical measurement of CO_2 as well as oxygen and other gases. Preliminary measurements performed on an adult volunteer (author) with the so-called "Microcell optical sensor" placed on the forearm and heated at 42°C have shown similar performance as that obtained with a

[4]Hayoz J, Schmid ER, Schmidlin D. Combined pulse oximetry and carbon dioxide tension ear sensor in adult patients early after cardiac surgery. EACTA 2002:34.

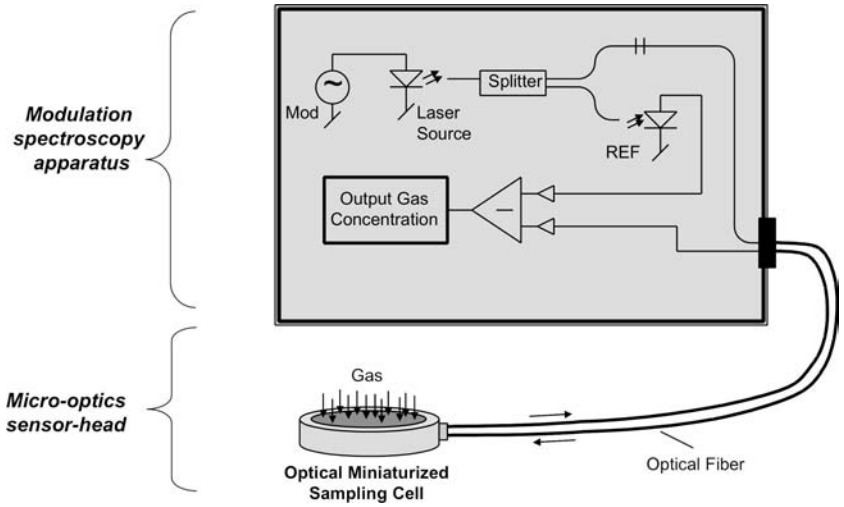

Figure 3. Optical transcutaneous blood gas measurement technique. Overview.

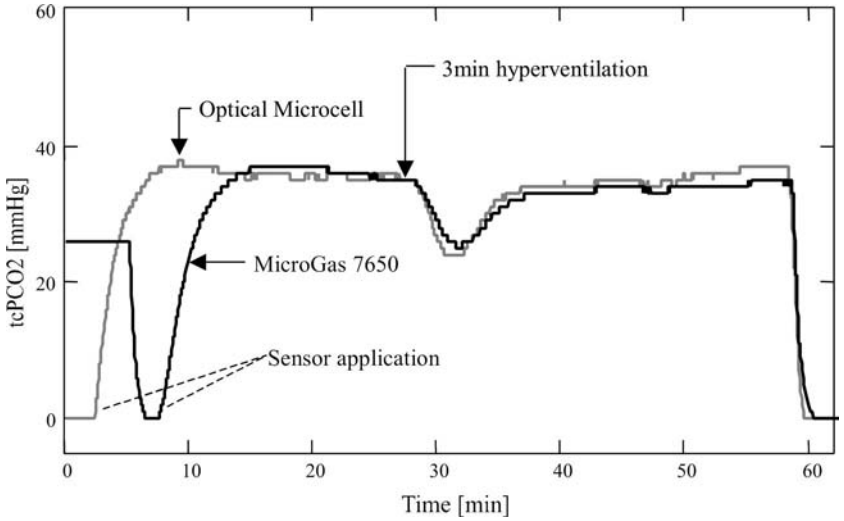

Figure 4. Comparative *in vivo* $tcPco_2$ measurements obtained with an optical Microcell system and a MicroGas.

commercially available electrochemical transcutaneous sensor (MicroGas 7650, Radiometer-Basel, Switzerland) (Fig. 4).

CONCLUSION

$tcPco_2$ sensors were introduced for clinical use about 20 yr ago. Initially, they were mainly used in neonatology together with the measurement of $tcPo_2$ and, more recently, in adult monitoring together with the measurement of Spo_2 to further specific applications, e.g., during mechanical ventilation, bronchoscopy, sleep studies, and pulmonary stress testing. The potentiometric CO_2 measurement technology has been continuously improved during the last two decades, making the $tcPco_2$ systems significantly easier and more reliable for use in clinical practice. It still requires for the regular re-membraning and calibration of the sensor. Preliminary results obtained with an optical-only CO_2 detection in the near-infrared light show that long-term stable and calibration-free CO_2 monitoring is possible. The same optical-only technology may also be applied to the measurement of other blood gas parameters, such as oxygen and anesthetic gases.

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Multiwavelength Pulse Oximetry: Theory for the Future

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BACKGROUND: As the use of pulse oximeters increases, the needs for higher performance and wider applicability of pulse oximetry have increased. To realize the full potential of pulse oximetry, it is indispensable to increase the number of optical wavelengths. To develop a multiwavelength oximetry system, a physical theory of pulse oximetry must be constructed. In addition, a theory for quantitative measurement of optical absorption in an optical scatterer, such as in living tissue, remains a difficult theoretical and practical aspect of this problem.

METHODS: We adopted Schuster's theory of radiation through a foggy atmosphere for a basis of theory of pulse oximetry. We considered three factors affecting pulse oximetry: the optics, the tissue, and the venous blood.

RESULTS: We derived a physical theoretical formula of pulse oximetry. The theory was confirmed with a full SO_2 range experiment. Based on the theory, the three-wavelength method eliminated the effect of tissue and improved the accuracy of Spo_2. The five-wavelength method eliminated the effect of venous blood and improved motion artifact elimination.

CONCLUSIONS: Our theory of multiwavelength pulse oximetry can be expected to be useful for solving almost all problems in pulse oximetry such as accuracy, motion artifact, low-pulse amplitude, response delay, and errors using reflection oximetry which will expand the application of pulse oximetry. Our theory is probably a rare case of success in solving the difficult problem of quantifying optical density of a substance embedded in an optically scattering medium.

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The principle of pulse oximetry was reported for the first time by Aoyagi and co-workers in 1974 (1,2). Thanks to the subsequent technical improvements by the Minolta and Nellcor Corporations, the use of pulse oximeters has spread worldwide and is contributing to a wide spectrum of medical practice. As the use of pulse oximeters increases, the needs for higher performance and wider applicability of pulse oximetry have increased as well. To realize the full potential of pulse oximetry, we propose that it is necessary to increase the number of optical wavelengths. To develop such a multiwavelength system, a physical theory of pulse oximetry must be constructed. The first physical theory of pulse oximetry was proposed by Shimada et al. (3). Since then many theories have been devised. No theory, however, has succeeded in improving pulse oximetry with an increased number of wavelengths. In this article, will explain our physical theory, how the theory has been experimentally proven, and how it can be practically used for improving the performance of pulse oximetry.

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SIMULATORS OF PULSE OXIMETRY

Katsuyuki Miyasaka, the chairperson of the Japanese ISO standards committee for pulse oximeters, proposed establishing a standard method for calibrating pulse oximeters. Minolta had such a pulse oximetry simulator and used it for the basic study of pulse oximetry principles (3). This device had a sample cell with a thickness of 3 mm with pulsation of 0.25 mm given by an external drive. The sample cell had transparent glass windows on both sides. When a pulse oximeter probe was attached to the sample cell filled with purified hemoglobin solution, the hemoglobin–oxygen saturation determined by the oximeter (Spo_2) was consistent with the actual hemoglobin–oxygen saturation (SO_2) of a hemoglobin solution. But when the sample cell was filled with blood, the Spo_2 over-estimated the SO_2 at $<90\%$. Yamanishi of Minolta and Aoyagi of Nihon Kohden together worked to improve the simulator to make the Spo_2 consistent with the blood SO_2. Many simulator modifications were tried, but ultimately the project did not succeed.

Several months later, John Severinghaus in San Francisco gave us data from pulse oximeter tests in human volunteer subjects. Data from one anemic test subject were of particular interest because of the error noted in Spo_2 determination at low saturation; a description of this error was later published by Severinghaus and Koh (4). To model anemia and other clinical issues in pulse oximetry, we constructed a

simulator with double layers of blood and milk separated by a transparent elastic diaphragm. With this simulator, the Spo_2 became consistent with the SO_2 of blood (5). From this experimental result, we noticed that tissue (milk in this last simulator) is a source of error in pulse oximetry. Later, we improved the simulator to be able to adjust the amplitude ratio of blood and milk. But when we noticed that venous blood was also a source of error, we gave up on making a pulse oximetry simulator.

OPTICAL ATTENUATION BY BLOOD

To realize the potential of multiwavelength pulse oximetry, we started to build a comprehensive theory of pulse oximetry. The straight incident light into the tissue is gradually scattered. This process is theoretically very complicated. We assumed the optics of pulse oximetry to be a field of completely scattered light. Then we adopted Schuster's theory of radiation through a foggy atmosphere (6). If we trace the light paths in Schuster's model in the opposite direction, the optical system is constructed with a small light source and wide light receiver. Therefore, we decided Schuster's theory could be applied to the theory of pulse oximetry. According to Schuster's theory, the following formula was obtained for the optical density change ΔA_b caused by the blood thickness change ΔD_b [cm] (7):

$$\Delta A_b = \sqrt{E_h(E_h + F)}\ \mathrm{Hb}\ \Delta D_b$$

where $E_h \equiv SE_o + (1 - S)\,E_r$; E_o and E_r are the extinction coefficients [$dL \cdot g^{-1} \cdot cm^{-1}$] of oxyhemoglobin and deoxyhemoglobin, respectively. S is oxygen saturation. Hb is hemoglobin concentration of the blood [g/dL]. F is a scattering coefficient [$dL \cdot g^{-1} \cdot cm^{-1}$]. We experimentally obtained the following result:

$$\Delta A_b = (\sqrt{E_h(E_h + F)}\ \mathrm{Hb} + Z_b)\Delta D_b$$

where Z_b [1/cm] is approximated not to depend on the wavelength and becomes zero when the optical receiver is wide enough.

ERROR SOURCES IN PULSE OXIMETRY

There are three factors affecting pulse oximetry: optics, tissue, and venous blood.

1. Optics: A straight incident light to tissue is scattered wavelength-dependently until about 2 mm depth (8). This phenomenon causes an error in Spo_2 when the inner structure of tissue is not uniform. To eliminate this effect, a thin optical scatterer must be attached to the incident side surface of the object.
2. Tissue: If the effect of tissue is considered, total optical density is as follows (9):

$$\Delta A = (\sqrt{E_h(E_h + F)}\ Hb + Z_b)\Delta D_b + Z_t \cdot \Delta D_t$$

where ΔD_t is the thickness change of the tissue [cm]. Z_t [1/cm] was approximated to be a constant independent of the wavelength. Therefore:

$$\Phi_{ij} \equiv \Delta A_i/\Delta A_j = \frac{\sqrt{E_{h_i}(E_{h_i} + F)} + E_{x_i}}{\sqrt{E_{h_j}(E_{h_j} + F)} + E_{x_j}}$$

$$E_{x_i} \equiv Z_b/Hb + Z_t\Delta D_t/(Hb\Delta D_b)$$

Experimentally E_{xj} has a little wavelength dependency as follows:

$$E_{x_i} = A_iE_{x_j} + B_i$$

where A_i and B_i were named tissue constants. There are two variables SaO_2 and E_{x_j} in this formula. If three-wavelengths are used, two simultaneous equations are obtained. A solution of the equations gives the Spo_2 without the effect of E_{x_j}.

3. Venous Blood: If the effect of venous blood is considered with the following equation (10):

$$\Phi_{ij} \equiv \Delta A_i/\Delta A_j = \frac{\sqrt{E_{a_i}(E_{a_i} + F)} + \sqrt{E_{v_i}(E_{v_i} + F)} \cdot V + E_{x_i}}{\sqrt{E_{a_j}(E_{a_j} + F)} + \sqrt{E_{v_j}(E_{v_j} + F)} \cdot V + E_{x_j}}$$

$$V \equiv \Delta D_v/\Delta D_a$$

The suffixes "a" and "v" mean arterial blood and venous blood, respectively. There are four variables SaO_2, SvO_2, V, and E_{x_j} in this formula. If five-wavelengths are used, four simultaneous equations are obtained. The solution of the equations gives Spo_2 without the effect of other variables.

THREE-WAVELENGTH PULSE OXIMETRY

To prove our hypothesis on the three-wavelength system, the following study was conducted (11): The wavelengths used were: $\lambda_1 = 805$ nm, $\lambda_2 = 890$ nm, $\lambda_3 = 660$ nm. The LEDs and the photodiode of the probe were attached inside and outside of the external ear, respectively. With informed consent and IRB approval, pairs of ΔA_is and SaO_2 measured with a CO-oximeter OSM3 (Radiometer, Copenhagen, Denmark) were obtained from chronic lung disease patients. Spo_2 was calculated with two methods. The first method was to solve the following simultaneous equations. This was named $3wSpO_2$.

$$\Phi_{12} \equiv \Delta A_1/\Delta A_2 = (\sqrt{E_{h_1}(E_{h_1} + F)} + A_1E_{x_2} + B_1)/(\sqrt{E_{h_2}(E_{h_2} + F)} + E_{x_2})$$

$$\Phi_{32} \equiv \Delta A_3/\Delta A_2 = (\sqrt{E_{h_3}(E_{h_3} + F)} + A_3E_{x_2} + B_3)/(\sqrt{E_{h_2}(E_{h_2} + F)} + E_{x_2})$$

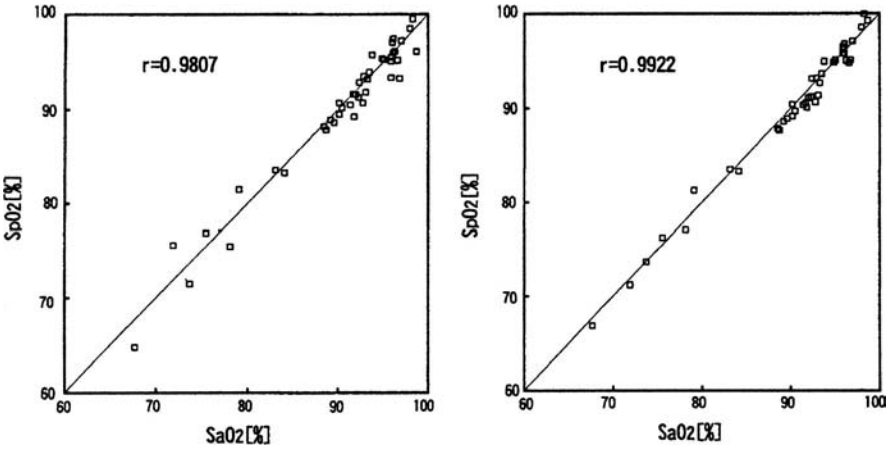

Figure 1. Comparison of two-wavelength Spo_2 (left) and three-wavelength Spo_2 (right) on the relationship between Spo_2 and SaO_2 determined with hemoximetry. Twenty-one patients with mild chronic lung disease were studied with (both techniques) a three-wavelength probe. Based on the same data two different calculations of Spo_2 were tried and compared.

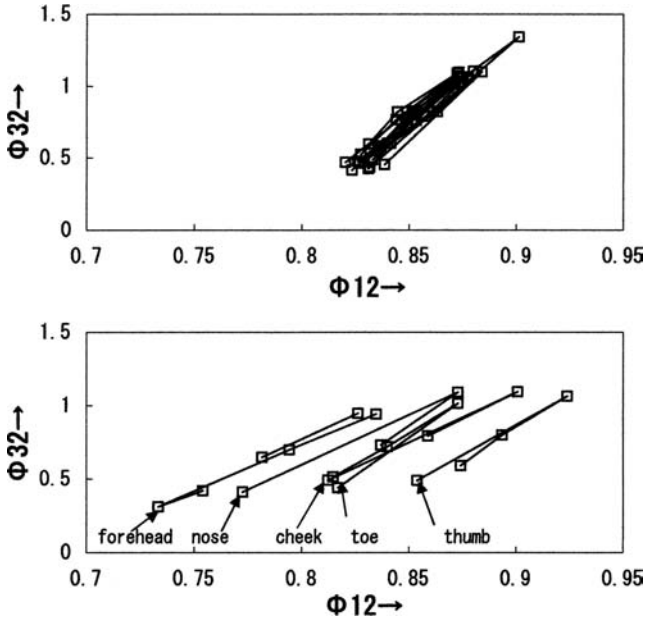

Figure 2. Transmittance and reflectance data. Upper graph shows data from the transmittance method (probe attached to thumb, middle finger, index finger, and toe) and the lower graph contains data from the reflectance method (probe located on forehead, nose, cheek, toe, and thumb). For details of experiment see text.

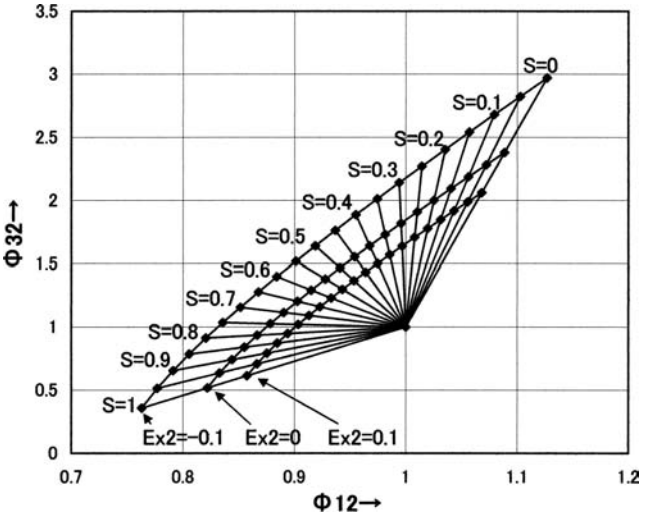

Figure 3. The relationship between Φ_{12} and Φ_{32} calculated from theoretical equations. See text for details.

Another method was to solve the equation of Φ_{32}. This was named $2wSpO_2$. In the calculation, effective E_{o_i} and E_{r_i} were used for E_{o_i} and E_{r_i} as follows:

$$\text{effective } E_{o_i} = \sum[(E_o(\lambda)L_i(\lambda)]/\sum L_i(\lambda)$$

$$\text{effective } E_{r_i} = \sum[(E_r(\lambda)L_i(\lambda)]/\sum L_i(\lambda)$$

where $E_o(\lambda)$, $E_r(\lambda)$, and $L_i(\lambda)$ are the spectrums of oxyhemoglobin, deoxyhemoglobin, and LED, respectively. The E_{x_2} for $2wSpO_2$ was selected to be zero. The combinations of tissue constants A_is and B_is for $3wSpO_2$ were selected so as to obtain the best correlation between SaO_2 and Spo_2. The result is shown in Figure 1. This result shows that the three-wavelength method improves the accuracy of Spo_2 when the constants A_is and B_is were appropriately selected.

REFLECTANCE PULSE OXIMETRY

A comparison of the transmitting method and reflectance methods was made using a volunteer (12). In the transmitting method, the probe was attached to the thumb, middle finger, index finger, and toe. In the reflectance method, the probe was attached to the forehead, nose, cheek, toe, and thumb. The volunteer was first asked to inspire O_2 gas, then breath-hold and finally to again inspire O_2 gas. The two groups of data were plotted on each plane with x-axis of Φ_{12} and y-axis of Φ_{32}, named Φ_{12}–Φ_{32} plane, as shown in Figures 2a and b. The O_2 gas data are the lowest ones for each probe site. The O_2 gas data of the reflectance method makes a straight line. The data on this line are calculated to $S = 1$ with the three-wavelength calculation. The O_2 gas data of the transmittance method also are on the line. Therefore, with the three-wavelength system, there is no substantial difference between the two methods.

FULL SO_2 RANGE EXPERIMENT

To confirm the reliability of the theoretical formula and to obtain tissue constants A_is and B_is, we conducted an experiment (13) as follows. The wavelengths used were: $\lambda_1 = 805$ nm, $\lambda_2 = 875$ nm, $\lambda_3 = 660$

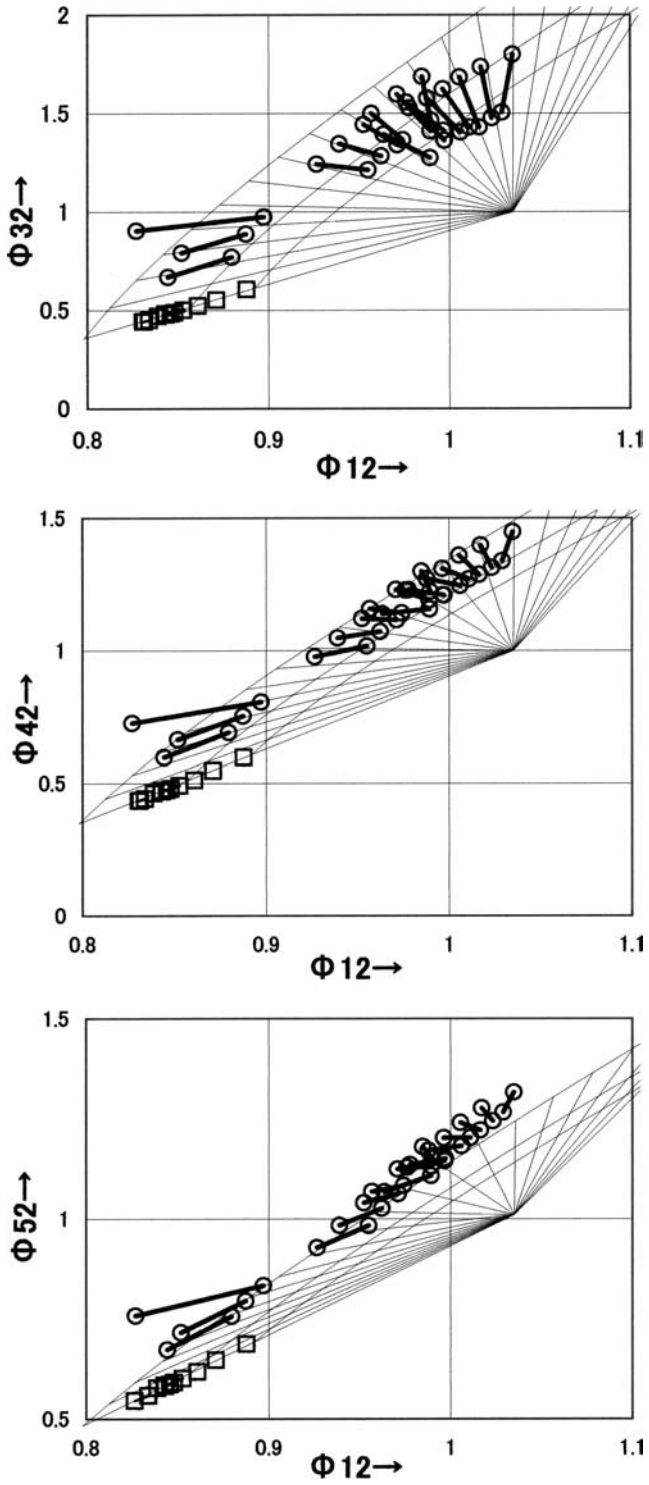

Figure 4. Grids with focus correction. The square symbols indicate oxygen inspiration data. The round symbols indicate low SO_2 data.

nm, λ_4 = 700 nm, and λ_5 = 730 nm. The photodiode size was 6 mm × 6 mm. Figure 3 shows a Φ_{12}–Φ_{32} relationship calculated based on the theoretical equations. The equi-SO_2 lines were drawn for each 5% from 100% to 0%. The equi-E_{x_2} lines were drawn for −0.1, 0, and +0.1. An approximation was made to be A_i = 1 and B_i = 0. The pattern made by these equi-SO_2 lines and equi-E_{x_2} lines was named "grid." The equi-SO_2 lines are like a Japanese folding fan and all cross at one point named "focus."

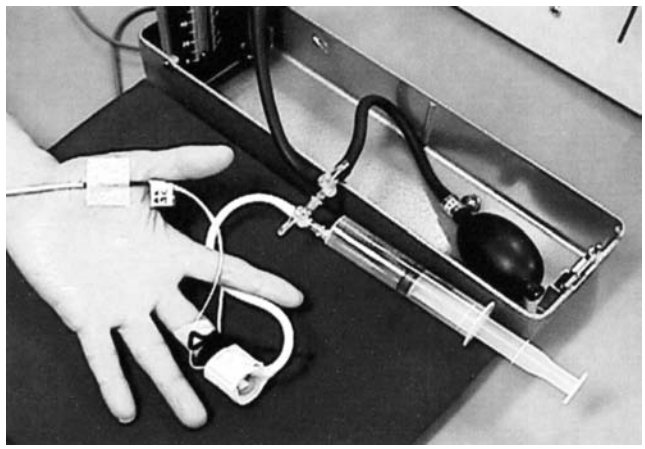

Figure 5. Apparatus used in deep SO_2 experiment.

What needed to be proved experimentally was the existence of the focus and location of the focus. For this purpose, SaO_2 must be changed far wider than the limit realizable with a volunteer experiment. Our method was as follows:

1. The LED and PD of a branch type probe were attached to a fingertip.
2. The finger was bound by a string to make the blood flow stop and to make the SO_2 of blood in the finger decrease gradually toward zero.
3. The finger was wrapped with a small air-cuff and the air pressure was pulsated to make the blood in the finger pulsate.
4. The baseline of the pressure was changed to high and low alternately to make the tissue tension change to make E_{x_2} change.
5. The fingertip was massaged between measurements to make the blood SO_2 uniform.
6. Φ_{12} and Φ_{32} were obtained at low pressure, at high pressure, and again at low pressure. The data of the two low pressures were averaged.
7. Each pair of points of the high pressure and low pressure on the Φ_{12}–Φ_{32} plane was joined with a straight line as an experimental equi-SO_2 line.

Another experiment with O_2 gas inspiration was made with young healthy volunteers. Φ's values were obtained with the hand in the up, horizontal, and down positions. This data point array on the Φ_{12}–Φ_{32} plane does not depend on the person and is an experimental equi-SO_2 line for SO_2 = 1.

The two SO_2 = 1 lines, one theoretical and the other experimental, were not coincident but in parallel. The theoretical grid was moved so as to harmonize the theoretical equi-SO_2 lines with experimental equi-SO_2 lines. The same was done for the Φ_{12}–Φ_{42} plane and Φ_{12}–Φ_{52} plane. The results are shown in Figure 4. The shift of the focus tells us the values of the tissue constants as follows: A_1 = 1.035, A_2 = A_3 = A_4 = 1,

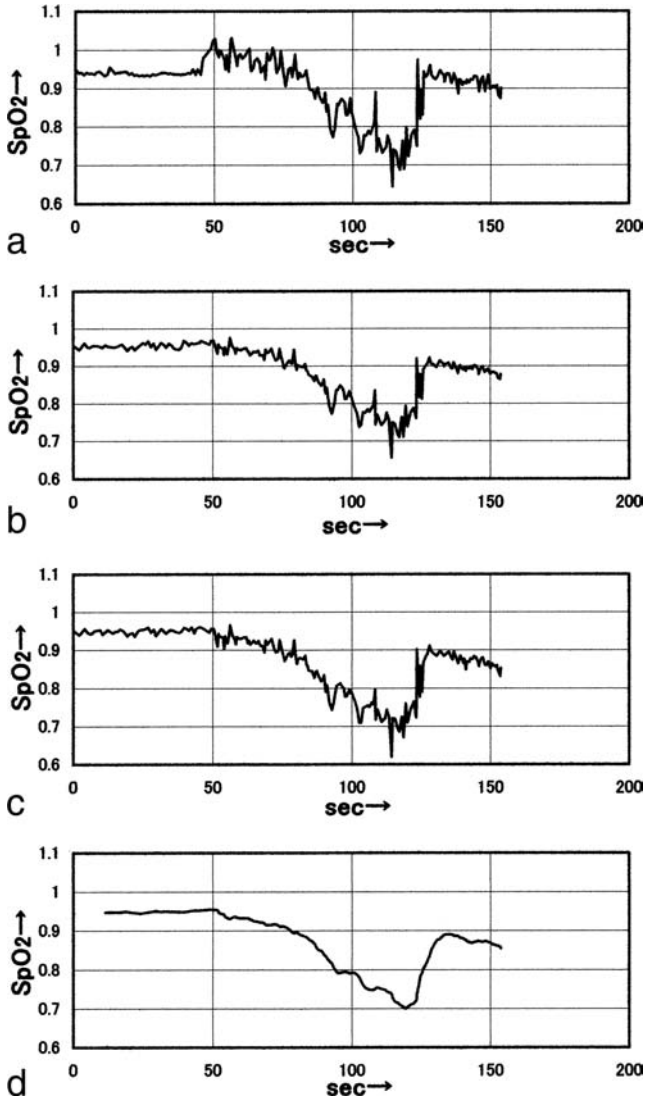

Figure 6. Examples of artifact elimination in three- and five-wavelength Spo_2 (panels b and c) compared with that in two-wavelength Spo_2 determination (panel a). In the lower panel (d) five-wavelength Spo_2 determination with smoothing is shown.

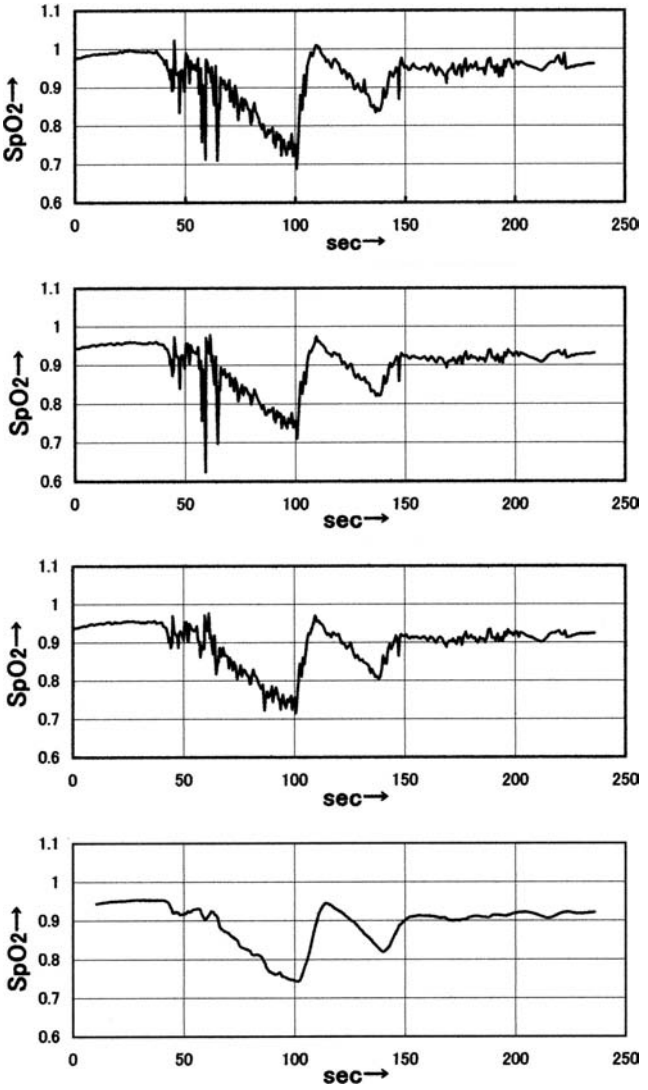

Figure 7. Another example of artifact elimination with multiwavelength Spo_2 determination. See also Figure 6.

$A_5 = 1.01$, $B_1 = 0.0141$, $B_3 = B_4 = 0$, $B_5 = 0.004$. The above-mentioned approximations were thus experimentally adjusted.

Since the E_{x_2} values of the experimental data are not consistent on the three planes, the E_{r_4} was corrected from 0.2777 to 0.31, and the E_{r_5} was corrected from 0.20411 to 0.245. The theoretical meaning of these corrections is a problem to be solved in the future. But the theory was confirmed and the tissue constants were obtained. Therefore, we can calculate Spo_2 with multiwavelength pulse oximetry. Figure 5 shows a picture of this deep SO_2 experiment.

ELIMINATION OF MOTION ARTIFACT

Motion artifact is conjectured to arise from the movement of tissue and venous blood. The five-wavelength system is supposed to be effective for elimination of motion artifact. Examples of motion artifact elimination are shown in Figures 6 and 7 (14). In both cases, the volunteer was in a supine position and the probe was attached to the right middle finger. The hand was down for Figure 6, and was horizontal for Figure 7. The volunteer was asked to move his hand in a chopping direction and to breath-hold for a short time. Figures 6a–c show $2wSpo_2$, $3wSpo_2$, and $5wSpo_2$, respectively. In Figure 6, there is considerable improvement from a to b. This is probably due to elimination of tissue effect. In Figure 7, there is considerable improvement from b to c. This is probably due to elimination of venous blood effect. The Figures 6d and 7d are running averages of $5wSpo_2$ with simple weighting. The patterns of Spo_2 are smooth with little time delay. These are successful examples, but motion artifacts can be difficult to eliminate. The total waveform of the artifact must be considered in order to improve the artifact elimination.

HISTORICAL CONSIDERATIONS

The quantitative measurement of optical absorptive substances in an optical scatterer has long been a

difficult problem (15). But our theory is probably a rare case of success in solving the problem. A change of the thickness of the object makes the problem easy to solve. This is originally Squire's idea (2) and is a concept that does not require expelling all of the blood in a body part such as with the approach used in Wood's ear oximeter (16). The above-mentioned effect of tissue was considered when we made the pulse oximetry simulator. The effect of venous blood on such models was reported by Goldman et al. (17).

Our theory of multiwavelength pulse oximetry may be useful for solving almost all problems in pulse oximetry such as accuracy, motion artifact, low pulse amplitude, quick response, and reflection method, which will expand the application of pulse oximetry.

There was an eight-wavelength ear oximeter [Hewlett-Packard model 47201 Ear Oximeter (Catalog)]. It had excellent accuracy comparable to a modern pulse oximeter. This method measures incident light and transmitted light at the ear lobe for eight-wavelengths and calculates SaO_2 with a rather simple *a-priori* formula. The constants in the formula were determined empirically from human data. This was an application of Robert Shaw's patent (18). Shaw says in his patent that the more the number of wavelengths, the more the accuracy will be improved. This may be true, but eventually too many wavelengths make the device impractical.

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APPENDIX: Symbol Definitions

A	Absorbance
A_i	Constant of the tissue
A_b	Absorbance of blood
B_i	Constant of the tissue [$dL \cdot gm^{-1} \cdot cm^{-1}$]
D	Thickness [cm]
E_a	Extinction coefficient of arterial blood [$dL \cdot g^{-1} \cdot cm^{-1}$]
E_v	Extinction coefficient of venous blood [$dL \cdot g^{-1} \cdot cm^{-1}$]
E_o	Extinction coefficient of oxyhemoglobin [$dL \cdot g^{-1} \cdot cm^{-1}$]
E_r	Extinction coefficient of deoxyhemoglobin [$dL \cdot g^{-1} \cdot cm^{-1}$]
E_h	Extinction coefficient of mixed hemoglobin [$dL \cdot g^{-1} \cdot cm^{-1}$]
E_x	Extinction coefficient of tissue [$dL \cdot g^{-1} \cdot cm^{-1}$]
F	Scattering constant [$dL \cdot g^{-1} \cdot cm^{-1}$]
Hb	Hemoglobin concentration [g/dL]
S	Oxygen saturation
V	Ratio of venous blood thickness change and arterial blood thickness change
Z_b	Optical density for 1cm thickness of the blood caused by small optical receiving area [1/cm]
Z_t	Optical density for 1 cm thickness of the tissue [1/cm]
Δ	Changed quantity
ΔA	Optical density change
ΔA_b	Blood optical density change
ΔD_a	Arterial blood thickness change [cm]
ΔD_b	Blood thickness change [cm]
ΔD_t	Tissue thickness change [cm]
ΔD_v	Venous blood thickness change [cm]
Φ_{ij}	$\Delta A_i/\Delta A_j$, so called ratio of ratios (AC/DC)/(AC/DC)

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Intrapartum Oximetry of the Fetus

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Fetal monitoring during labor aims to identify fetal problems which, if uncorrected, may result in morbidity or death. A nonreassuring or abnormal fetal heart rate trace by cardiotocography (CTG) does not necessarily equate with fetal hypoxia and/or acidosis. However, in the absence of more objective data, the use of CTG often results in variable, but inappropriately high, operative delivery rates (forceps, vacuum, or cesarean delivery) for nonreassuring fetal status in many hospitals. The addition of fetal pulse oximetry (FPO) has the potential to improve the assessment of fetal well-being during labor. In this review we consider several aspects of FPO. Several factors, such as sensor to skin contact, uterine contractions, fetal hair, and caput succedaneum, influence the performance and use of FPO. Issues such as clinicians' perspectives of FPO sensor placement, maternal perspectives of FPO during labor, and an economic analysis have all favored FPO. Several randomized controlled trials (RCTs) of FPO reported a reduction in cesarean delivery for nonreassuring fetal status when FPO was added to conventional CTG monitoring, with no difference in overall cesarean delivery rates. One large RCT reported no difference in mode of birth for any indication. Several issues relevant to the future of FPO have been addressed by these RCTs, the major issue being that it makes no difference to cesarean rates. It may be argued that FPO has a valid clinical use in monitoring the fetus with congenital heart block. Additionally, in situations of nonreassuring fetal status and dystocia, FPO may provide the necessary reassurance until adequate resources for cesarean delivery are available.

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The aim of fetal monitoring during labor is to identify fetal problems which, if uncorrected, may result in morbidity or death. The fetal heart rate and uterine contractions may be recorded by using cardiotocography (CTG). Although there is no universal agreement on the interpretation of these patterns, several groups have published guidelines [for example, the American College of Obstetricians and Gynecologists (1); The Royal Australia and New Zealand College of Obstetricians and Gynaecologists (2); and Royal College of Obstetricians and Gynaecologists (3)]. Reassuring patterns require no specific action. Nonreassuring patterns occur in approximately 15% of monitored labors (4,5), and may prompt clinical actions ranging from simple maneuvers, such as a change of maternal position, to expedited birth of the baby. Ominous patterns usually prompt expedited birth with the aim of preventing or minimizing hypoxia in the fetus. The positive predictive value of CTG for adverse outcome is low and the negative predictive value is high (4). Thus, while a normal CTG usually indicates reassuring fetal status, a nonreassuring or abnormal CTG does not necessarily equate with fetal hypoxia and/or acidosis. These features, combined with marked interobserver variation in CTG interpretation (6), result in variable, but inappropriately, high operative delivery rates (forceps, vacuum, or cesarean delivery) for nonreassuring fetal status in many hospitals.

Once a nonreassuring fetal heart rate pattern has been identified during labor, a number of additional assessments of fetal well-being may be considered. These aim to improve the intrapartum assessment of fetal well-being and thereby safely reduce operative delivery rates for nonreassuring fetal status associated with conventional monitoring by CTG. They do not replace the CTG, but are usually complementary to it, either intermittently or continuously. One such test is fetal pulse oximetry (FPO or $FSpo_2$).

Pulse oximetry of functional oxyhemoglobin and deoxyhemoglobin saturation is widely used in the adult and pediatric clinical setting (7). FPO has developed to accommodate the issues specific to the fetal environment, with the use of reflectance pulse oximetry in some systems: the light-emitting diodes and photodetector are housed in the same plane of the sensor, thus relying on backscattered or reflected light,

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rather than the transmitted light used in conventional oximeters (8,9).

Several investigators have reported clinical studies with prototype oximetry systems (10–20). At least three systems have been developed to commercial status. OB Scientific (Germantown, WI) markets a sensor, shaped like a tongue depressor, which slides along the fetal torso during a vaginal examination in labor, with or without ruptured amniotic membranes. Nonin Medical Inc. (North Plymouth, MN) incorporates pulse oximetry into a fetal scalp electrode. The Nellcor OxiFirst™ system (sometimes referred to as the Nellcor N-400 system) has a sensor that is directed to lie against the fetal temple or cheek during a vaginal examination in labor, after rupture of the amniotic membranes (TYCO Inc., Pleasanton, CA).

Numerous reviews have considered the adaptation of conventional pulse oximetry to the fetal environment, including sensor design, calibration issues, and clinical applications (21–26). This review provides a brief overview of factors influencing the performance and use of FPO and discusses several randomized controlled trials (RCTs) of FPO, along with issues such as clinicians' perspectives, maternal perspectives, and economic analysis. The future of FPO is also considered.

FACTORS INFLUENCING THE PERFORMANCE AND USE OF FPO

Potential Artifacts in FPO

Sensor to Skin Contact and Uterine Contractions

A report that $FSpo_2$ decreased after uterine contractions, using early prototype sensors (27), may have been confounded by artifact from inadequate contact between the sensor and fetal skin (28). The Nellcor N-400/FS14 system incorporated a complex algorithm for assessing signal quality and suspended $FSpo_2$ display when the sensor lost contact with fetal skin (Nellcor internal data). East et al. (29) demonstrated a significant difference in mean signal quality of only five signal quality units (of a possible 100) with this oximetry system in the 30 s before intrauterine pressure catheter-monitored contractions and during noncontraction periods. This was noted in conjunction with a mean decline of 2.3% $FSpo_2$ during contractions to 45% after contractions, a magnitude that is unlikely to be of any clinical importance (29). Episodes of excessive force on the sensor, such as may occur during uterine hyperstimulation (30) and reported with tightly affixed neonatal oximetry (31), were not identified in this study. Such conditions require further evaluation to determine their potential influence on detection and accuracy of $FSpo_2$ values. While the use of the Nonin system's spiral electrode on the fetal head may not be susceptible to direct pressure artifact from uterine contractions, stasis of scalp blood may be another source of artifact.

Fetal Hair

The presence of dark, thick, curly hair may make sensor attachment difficult (32), or may be a source of artifact, as it absorbs red light and affects the error/signal ratio (33). Optical shunting may also occur with lightly colored hair (34), although not all investigators have found a difference in $FSpo_2$ values recorded from the scalp of babies with fair or dark hair (10). Nijland et al. (35) found no difference between $FSpo_2$ values obtained from shaved and unshaved skin of fetal lambs. The Nellcor and OB Scientific FPO systems generally avoid areas of fetal hair, thereby avoiding this source of artifact. Reports of how the Nonin system deals with this issue are yet to emerge in the literature.

Caput Succedaneum

Early reports of FPO recorded using modified adult oximeters, not calibrated for the fetal environment, suggested that when FPO values could be recorded from caput, they were significantly higher than those recorded where no caput was present (36,37). One consideration was that the plethysmograph registered by the oximeter over caput may have come from venous pulsation, or from artifact as the arterial signal passed through the congested or edematous scalp (37). These findings contrasted with those of Knitza et al. (10), who noted no difference in $FSpo_2$ values in babies born with or without caput. The Nonin system evolved from the sensor initially used by Knitza et al. (10). Details of the potential effect of caput on $FSpo_2$ values when using this system are not currently available. By placing the FPO sensor on the fetal temple or cheek (Nellcor system) or back (OB Scientific system), this potential for artifact has been avoided by other manufacturers.

Critical Threshold Fetal Oxygen Saturation Values

Animal and human research suggests that when using sensors with 735 and 890 nm wavelengths, preductal FPO values $\geq$30% are considered reassuring (38–40). When $FSpo_2$ values are reassuring, even in the presence of a nonreassuring CTG, it is considered appropriate to continue labor unless otherwise indicated (Fig. 1).

There are several recommendations as to how long to allow $FSpo_2$ values $<$30% to continue before intervening. Proposed durations include between consecutive contractions (approximately 1 min) (41), 2 min (42), 10 min (43), or after cumulative episodes of low $FSpo_2$ (44). Data from the FOREMOST randomized trial (45) suggest that an average $FSpo_2$ $<$30% for 10 min may predict fetal scalp blood pH $<$7.20 (5). The fetus is usually not at risk from short periods of hypoxia, as there is preferential redistribution of cardiac output to the brain, heart, adrenals, and blood flow to the placenta (46). With prolonged hypoxia, however, compensatory mechanisms become inadequate, resulting in reduced cardiac output and blood

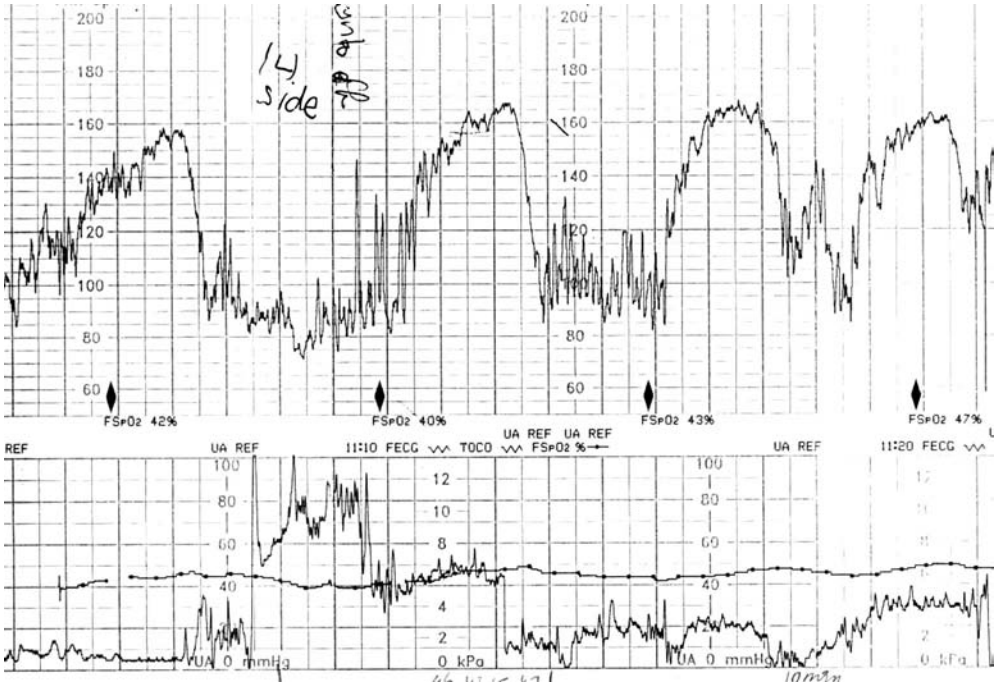

Figure 1. Nonreassuring cardiotocograph with reassuring fetal oxygen saturation values. Fetal oxygen saturation ($FSpo_2$) values are represented by the beaded line printed on the lower graph, (scale 0–100) and printed intermittently at the lower edge of the fetal heart rate graph. Paper speed 1 cm/min. Note that some values are absent at the beginning of this trace: $FSpo_2$ values are not recorded if there is no contact between the FPO sensor and the fetal skin, or if the signal is of inadequate quality. A fetal scalp pH taken several minutes later was 7.32.

pressure, with consequently reduced cerebral blood flow (47). This severely limits oxygen delivery to the brain and resultant neural damage (48). Appropriate interventions to avoid such sequelae may include maternal position change, to urgent birth via cesarean delivery (39,41,43). Clinical reports and research guidelines note that when the CTG is ominous, for example, in the presence of severe variable decelerations, the CTG is a better predictor of poor outcome than $FSpo_2$ values that would usually be reassuring (41,49). Further exploration into the ability of the fetus to sustain reassuring $FSpo_2$ values in such circumstances may not be feasible in the human setting. Rather, clinical expertise in CTG interpretation and initiating appropriate intervention are recommended in these circumstances (41). As for most clinical situations, assessment of fetal well-being during labor is best achieved through a combination of numerous considerations, rather than only the CTG or only $FSpo_2$ values.

These data represent an action threshold for preductal $FSpo_2$ values measured with the Nellcor system. An action value of 30% may be too conservative in a breech fetus, because postductal $FSpo_2$ values are lower than those from the preductal regions (50,51). The Nonin system measures preductal saturation (fetal scalp), whereas postductal $FSpo_2$ is measured from the torso when using the OB Scientific sensor.

The critical threshold for FPO using wavelengths typical of those used in neonates and adults is unclear, given the differences in $FSpo_2$ values returned when different wavelengths are used (52). Knitza et al. (53) reported a pilot study using the Nonin system (wavelengths 661 and 905 nm). They suggested that $FSpo_2$ of 25%–30% represented fetal hypoxia. The OB Scientific system uses wavelengths of 660 and 890 nm (9). Luttkus et al. (54) used this system to compare $FSpo_2$ values $<30\%$ or that declined by $>20\%$, with ST events recorded from a fetal electrocardiogram. Desaturations occurred more frequently in fetuses with ST segment changes (54).

RCTS OF FETAL OXIMETRY

Five published RCTs have examined the clinical effectiveness of FPO using the Nellcor system. Four studies randomized laboring women whose fetuses demonstrated nonreassuring fetal heart rate tracings by CTG into two groups: in one group, continuous conventional fetal monitoring by CTG was used (CTG-only group) and, in the other group, FPO was added to CTG monitoring (CTG + FPO group) (55–58). Prespecified primary outcomes included cesarean delivery or operative birth (cesarean, forceps, or vacuum) for nonreassuring fetal status. All studies considered overall cesarean rates and other maternal and fetal/neonatal outcomes.

Before randomization, all participants in the Kuhnert and Schmidt trial (56) had fetal scalp blood sampling. By implication, those with nonreassuring fetal scalp blood findings would have proceeded to operative delivery, rather than study entry. It could,

Table 1. Selected Entry Criteria and Outcomes From Randomized Trials of Fetal Oximetry

Study	Entry criteria	*N*	Action threshold $FSpo_2$	Outcome	RR*	CI
Garite et al. (55)	Nonreassuring	1010	<30% for entire interval between contractions	Cesarean delivery—all	1.12	0.91–1.37
	CTG			Cesarean delivery for NRFS	0.45	0.28–0.72
	Gestation ≥36 wk			Umbilical arterial pH <7.00	1.35	0.30–6.00
				NICU admission	1.14	0.87–1.49
Kuhnert and Schmidt (56)	Nonreassuring CTG	146	<30% for ≥10 min or repeatedly <30%	Cesarean delivery—all	1.13	0.46–2.75
	Fetal blood sampling			Cesarean delivery for NRFS	0.03	0.00–0.44
	Gestation ≥36 wk			NICU admission	1.00	0.30–3.31
Klauser et al. (57)	Nonreassuring CTG	327	<30% for >3 min	Cesarean delivery	0.93	0.76–1.14
	Gestation ≥28 wk			Cesarean delivery for NRFS	0.89	0.64–1.24
				Umbilical arterial pH <7.00	0.13	0.01–2.41
				NICU admission	0.94	0.55–1.63
East et al. (58)	Nonreassuring CTG	600	<30% for 10 min	Cesarean delivery	0.95	0.80–1.13
	Gestation ≥36 wk			Cesarean delivery for NRFS	0.69	0.48–0.99
				Umbilical arterial pH <7.00	0.88	0.13–6.22
				NICU admission	0.79	0.33–1.88
Bloom et al. (59)	Intrapartum CTG	5341	<30% for entire interval between contractions	Cesarean delivery	0.96	0.87–1.04
	Gestation ≥36 wk			Cesarean delivery for NRFS	0.91	0.75–1.09
				Umbilical arterial pH <7.00	2.05	0.51–8.20
				NICU admission	0.88	0.70–1.11
Bloom et al. (59) subgroup	Nonreassuring CTG	2168		Cesarean delivery	1.02	0.90–1.15
	Gestation ≥36 wk			Cesarean delivery for NRFS	0.89	0.70–1.14

CI = confidence interval; CTG = cardiotocograph; NRFS = nonreassuring fetal status; NICU = neonatal intensive care unit.

* Relative risk (RR) calculated from published event rates: cardiotocograph + fetal pulse oximetry compared with cardiotocograph only (with or without masked oximetry).

therefore, be considered that these fetuses were not exhibiting evidence of nonreassuring fetal status at the time of study entry, in contrast to those who were, based on the nonreassuring CTG only, as for the remaining studies (55,57,58).

Entry criteria to the study by Klauser et al. (57) included gestation from 28 wk, in contrast to the other reported studies, where only women of gestation ≥36 wk were included (55,56,58). Fetal monitoring of premature fetuses is more challenging to interpret than in the term equivalent. The report did not provide outcomes by gestational age (57).

The fifth and largest RCT (n = 5341) examined whether knowledge of FPO values influenced cesarean delivery rates in laboring women with CTG monitoring (59). All consenting women had a FPO sensor placed, then were randomized to have the $FSpo_2$ values displayed (open group) or blinded (masked group). The primary outcome was cesarean delivery. Some outcomes from a subgroup of those with a nonreassuring CTG before randomization were provided.

Given the heterogeneity among the five RCTs and the pending update of a systematic review (60), meta-analysis of these RCTs has not been presented here. Relevant findings from each trial are presented in Table 1. The substantive finding of these trials is dominated by the largest RCT, which concluded that knowledge of $FSpo_2$ values did not reduce overall cesarean delivery rates.

After delivery, neonatal outcomes were not different between the CTG-only or masked FPO group and the CTG + FPO group (55–59). Very large sample sizes would be required to detect between-group differences in low-prevalence adverse outcomes, such as meconium aspiration, neonatal encephalopathy, or long-term neurodevelopmental delay. Such adverse events were closely monitored within the FOREMOST trial (45), with all adverse maternal and neonatal events in both study groups reported to the Data Monitoring Committee, regardless of their likelihood of resulting from trial participation. Very few events occurred, despite all participants requiring a nonreassuring fetal status before study entry. No events resulted in changes to the trial protocol (58). The lack of between-group differences for outcomes such as umbilical arterial pH <7.00, low Apgar scores, or admission to the neonatal intensive care unit, provides some reassurance that delaying or averting operative

intervention during labor did not compromise these babies' outcomes.

Compliance with trial protocol was not well reported in the RCTs. Any variable monitored during labor would, at best, form only part of the overall clinical picture. Although the documented indication for cesarean delivery may have been nonreassuring fetal status, it remains unclear whether such an indication was actually informed by $FSpo_2$ values or by the CTG and other factors such as the degree of meconium staining of the amniotic fluid, for example. The conclusion of one study that knowledge of $FSpo_2$ values did not reduce cesarean rates (59) may reflect only a part of the overall picture. The question may be: "Did clinicians trust the validity of the $FSpo_2$ values?"

FURTHER CONSIDERATIONS OF FPO

If FPO makes no difference to cesarean rates, does it make any meaningful differences for other relevant clinical outcomes, or to clinicians, childbearing women, and the health dollar?

Further Clinical Outcomes

Several reports demonstrated that the addition of FPO in cases of complete congenital fetal heart block (CCHB) provided an important variable of fetal well-being (61–63). In the fetus with CCHB, the CTG usually records the fetal heart rate at approximately 70 bpm, without the typical heart rate fluctuations and responses to labor seen in other babies. Cesarean delivery is often offered, rather than labor with the uncertainty of fetal well-being. As an example, we monitored two fetuses with CCHB. FPO provided additional information about fetal condition, resulting in vaginal births of these babies (63).

Clinicians' Perceptions of Sensor Placement

An important, although often overlooked, consideration of new technology is ease of use and utility for the relevant clinician: for fetal oximetry, this includes nurses, midwives, and obstetric medical personnel (64). Johnson (33) evaluated operators' scores for fixation of early prototype sensors fixed to the fetal scalp by glue or suction and found that neither rated well. These findings prompted the development of new prototypes: neither method of fixation is currently used. Several investigators have reported that clinicians rated ease of Nellcor FPO sensor placement favorably (64–66).

Childbearing Women's Perceptions of FPO

An equally important aspect of technology development is an evaluation by those to whom it is applied. In the case of FPO, childbearing women provide valuable feedback on factors such as level of comfort during sensor placement and ongoing use, in addition to the potential for this form of monitoring to limit their ability to move freely during labor (45,67–69). Women's perceptions of their experience with labor and fetal monitoring were compared for the CTG-only and CTG + FPO groups in the FOREMOST randomized trial (45). The addition of FPO technology did not affect women's perceptions of fetal monitoring or their labor when there was already some concern about fetal well-being. Put another way, the trade-off between additional technology during labor was acceptable when the option of avoiding a cesarean delivery was considered (45).

Economic Considerations

The American College of Obstetricians and Gynecologists expressed concern that the addition of FPO would potentially increase costs without necessarily improving clinical outcomes (70). One RCT included a cost-effectiveness analysis of the prespecified primary outcome; operative delivery for nonreassuring fetal status (58). Rather than increasing costs, it demonstrated a saving of $813 (Australian dollars) for each operative delivery averted by the use of FPO (71). Although presented here with caution due to the inherent biases of *post hoc* analyses, reconstruction of the economic analysis to examine the small, nonsignificant difference in overall cesarean rates demonstrated an even greater saving for each cesarean delivery averted in the FPO group (71).

FPO: THE FUTURE

The future of FPO may have already been decided by two factors. The recent publication of a large RCT that demonstrated no difference in cesarean delivery rates is compelling (59) and the manufacturers of the oximetry system used in this and all other published RCTs have discontinued production of the system.

Several issues still warrant consideration before FPO are disregarded as a potentially useful adjunct to intrapartum fetal monitoring. The published RCTs required varying entry criteria and considered different action algorithms, with compliance not well reported, as well as considering different primary outcomes. Have the right questions been addressed by these RCTs? Has the right clinical management protocol been proposed and evaluated? Could pre- and postductal FPO measured by systems other than the Nellcor system, which have not yet been evaluated in RCTs, influence the clinical protocol and outcome(s)? Does FPO have a place, albeit limited, in clinical practice? Several high-quality RCTs demonstrated a reduction in cesarean delivery for nonreassuring fetal status in the CTG + FPO group compared with the CTG-only group with similar trial entry criteria (55,58). This finding is important, even though there was no difference in these trials for overall mode of birth, as a result of more cesarean deliveries, forceps, or vacuum births being conducted due to dystocia or inadequate progress. Avoidance of an emergency intervention for the sake of the baby has implications in terms of stress levels for the mother and resource implications for the health service providers: these outcomes have not yet

been evaluated in the RCTs. An "inevitable" operative birth (that is, for dystocia or inadequate progress) may be conducted when the woman has had more time to consider her options and when staffing levels can be adjusted over a number of hours rather than providing immediate staffing for an emergency cesarean.

The incidence of cesarean delivery for dystocia almost doubled in the RCT reported by Garite et al. (55) when FPO was added to CTG monitoring. Concerns were raised that the presence of the FPO sensor may have contributed to this outcome. Rates of cesarean for dystocia in the study by Bloom et al. (59), for which all participants had an FPO sensor, approximated those in the FPO group of the Garite et al. trial (55). The Nellcor sensor used in these trials was advanced through the cervix to lie against the fetal temple or cheek. Use of the OB Scientific sensor, placed through the cervix to lie against the fetal torso, compared with the Nonin system that attaches to the fetal head, may inform the unresolved question of the potential effect of an intrauterine sensor on dystocia.

Further exploration is recommended into the effect of a change in $FSpo_2$ in the individual fetus, in addition to a critical action threshold. Timing of the intervention (such as cesarean delivery) may be more important than currently realized and may only be considered in very large trials. Additionally, the clinical reports using the Nonin and OB Scientific FPO systems are still emerging. The different measurement locations and sensor designs may impact on clinical protocols in observational and randomized trials.

The value of intrapartum FPO for monitoring the fetus with CCHB may also be appropriate (63).

CONCLUSION

Intrapartum FPO initially emerged as a promising technology to assist in the assessment of fetal well-being. Well-conducted RCTs demonstrated no effect of the addition of this technology on overall modes of birth or neonatal outcomes, suggesting that this technology will not make a valid contribution to future fetal monitoring. That conclusion may be premature, given the remaining unanswered questions of its place in intrapartum fetal monitoring.

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Development of a Standardized Method for Motion Testing in Pulse Oximeters

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BACKGROUND: Pulse oximeter performance in the presence of motion varies among devices and manufacturers because of variations in hardware, software, testing, and calibration. Compounding these differences is a lack of uniform characterization of motion, and the consequential effects of motion upon the wide range of normal and abnormal human physiology. Traditional motion testing attempts to standardize motion into a reproducible form by using a mechanical jig to produce passive motion of a known amplitude and frequency. This type of motion challenge fails to account for the physiologic changes induced by active movement.

METHODS: We postulate that a more appropriate method for testing the performance of pulse oximeters in the presence of motion is to create a feedback control loop between the device and the test subject, providing a reproducible, actively created, and controlled motion test suitable for standardized testing among manufacturers. It is hoped that relying on a signal as seen from the oximeter's perspective will enable the creation of a sensitive and reproducible test method capable of separating those oximeters that can reject motion artifact from those that cannot.

RESULTS: Preliminary results have concentrated on building the tools and clinical protocols needed to evaluate this method. Some basic observations are reported, but insufficient numbers of experienced subjects precludes rigorous conclusions.

CONCLUSION: We have set the stage for a feasibility demonstration using a novel form of testing. With sufficient subjects and proper statistical evaluation, a robust test method for assessing the performance of pulse oximeters in the presence of motion may be at hand.

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In an ideal world, the performance of a medical device is fully characterized and understood before it becomes a standard of care. In pulse oximeters, the complex interaction between photons and tissue is not fully understood, leading to uncertainty in the true value of oxygen saturation. The accuracy specifications are stated as a range of acceptable values to account for some variation in human phenotype, and are at best an approximation, or "best fit" calibration. This situation is exacerbated by a historical lack of a standard method to calibrate and report performance. Despite these shortcomings, oximeters provide an invaluable vital sign in clinical monitoring, and therefore are considered a standard of care in many areas of medicine.

Assessing the uncertainty of pulse oximeters, independently characterizing their performance, has been a continuing quest of many researchers since modern oximeters first appeared on the market. The application of powerful microprocessors, modern signal processing theory, and improved electronics have enabled the current generation of oximeters to more reliably report saturation values. The new generation of pulse oximeters is able to obtain valid data despite noise and motion artifacts, and is capable of detecting ever smaller signals, thereby differentiating themselves from "first generation" oximeters (1) and intensifying the need for more powerful standardized performance assessment tools. An overview of pulse oximeter technology and testing is given by Jopling et al. (2). Issues that need to be investigated and resolved include the best method to assess accuracy, what effects contribute to calibration differences between brands, and actual performance under conditions of motion and perfusion metrics.

In this article we report the initial work to develop methods to assess motion performance claims on motion tolerance, state clearly the assumptions of the methods, and gather evidence to validate those assumptions. It is a collaboration among the United

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States Food and Drug Administration, academic anesthesiologists, and pulse oximeter manufacturers, with the goal of understanding and documenting the basic clinical performance of pulse oximeters.

BACKGROUND ON MOTION TESTING

The American Society for Testing and Materials (ASTM) pulse oximeter committee (composed of manufacturers, clinicians, and public representatives/regulators) wrote its first pulse oximeter standard, F1415, in 1987, which was adopted by the International Standards Organization (ISO) and the European Committee for Standardization. This draft had no requirements for motion artifact performance. In 1997, the ASTM committee was reconvened to update the standard, finally producing ISO 9919:2005/IEC 60601-2-54 in 2005. Even as evidence of the impact of motion was being published (3–5) the standard was still not able to establish definitions for motion types, a normative requirement for what constitutes motion tolerance, and a standardized method for testing motion resistance claims. The only requirement with respect to motion tolerance calls for disclosure of each manufacturer's test method. The consequence is that performance between brands may not be comparable. The ASTM pulse oximetry committee recognized this deficiency and launched an effort to develop the necessary test method.

As a prototype model of the motions seen in the clinical environment, and to construct a starting point to develop a test method, the Committee defined five types of motion to be used as exemplars: wave, scratch, clasp, tap, and squeeze. These are defined as follows.

1. Flexing or waving of the wrist and forearm with the elbow resting on a countertop
2. Scratching or rubbing motion of the fingertips against the countertop (the rest of the extremity should remain relatively motionless)
3. Flexion-extension of the fingers ("clenching" of the hand) but without pressing against a surface (the elbow is stationary against a countertop and the arm is held perpendicular to the floor)
4. Squeezing the "test" hand around a firm rubber handle, while compressing the tips of the fingers against the rubber handle with a force similar to that used to grip a handrail
5. Tapping the fingers of the "test" hand against the countertop

These were not intended to be the definitive set of motions, as little research has been published to fully characterize the clinical environment, but instead were postulated to span the range of motions seen (6). Further work is needed to qualitatively characterize these motions so that they may be reproducibly communicated. It is recognized that low perfusion and desaturation can add to the motion challenge (7), but the main focus here is to identify the issues that influence testing using relatively simple room air tests.

METHODS

We propose a test method for motion tolerance that relies on controlling the signal that the pulse oximeter sees internally rather than imposing an external constraint. Although traditional motion testing was performed by externally generating the motion of an appendage, for example, by placing the hand in a mechanical jig (4,8,9) or adding volunteer reference motion to recorded signals (10), this new approach uses the raw plethysmogram, the actual data stream collected and analyzed by the oximeter, as an indicator of the intensity of the external motions. We hope that this method will produce a more sensitive and realistic assessment of an oximeter's ability to maintain accuracy in the presence of motion.

We intend to use a pulse oximeter probe as a plethysmographic measuring tool on one finger of the hand in motion to measure, control, and modulate motion intensity with devices under test (DUT) on the remaining two fingers. In this way, we hope to present an equivalent motion challenge to all three fingers on the test hand. The resulting saturation values recorded will be compared with reference saturations from a stationary hand. Measurements taken with the subject motionless are considered the rest signal, in that the only pulsations measured are those generated by arterial pressure wave forms. Measurements taken during periods of motion constitute signal plus noise because of the confounding effect of motion artifact overlaying the signal. Our goal is to find an expression for this signal that is proportional to the level of motion intensity. As the level of motion rises, we would like the test signal to rise accordingly and not be a function of the absolute amplitude of the plethysmogram, which is predominantly a "DC" or static signal (not time varying).

Several candidate signals were explored, including:

1. The ratio of the alternating component (AC) to DC value computed using a Fourier transform over a short period, say 3–5 s
2. The ratio of the short-term pulse amplitude, calculated as a local maximum − minimum (3–5 s), to the longer term average (30 s). This is representative of the "perfusion index" (PI) used by several manufacturers but only acts on the infrared (IR) signal
3. The root mean square energy
4. The smoothed plethysmogram itself

We intend to use this signal in a closed-loop feedback arrangement, taking advantage of the test subject's ability to modulate their own level of motion activity and cause the plethysmogram to adjust in proportion (Fig. 1). The subject adjusts their intensity of activity in response to the visual presentation of

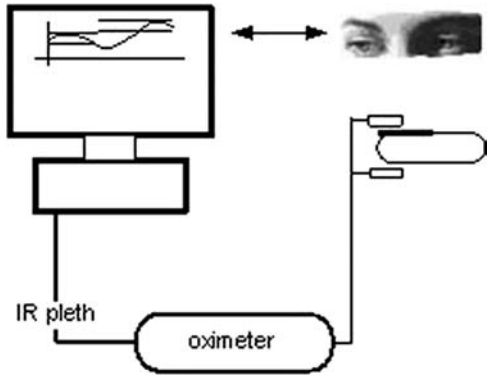

Figure 1. Subject sees the test signal presented on the monitor and the desired level. The subject adjusts their level of intensity (exertion levels) to keep it within the control limits.

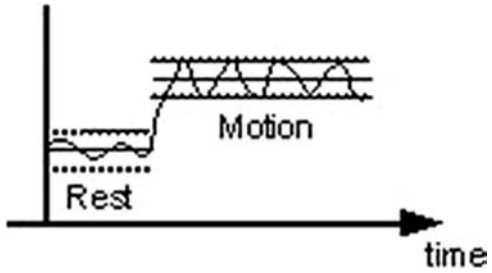

Figure 2. Subject is exerting sufficient activity to keep the test signal in the desired range.

their plethysmogram (or the selected function of the plethysmogram) to the desired target level.

Within this setup, we define A as the ratio of the test signal in a motion period to a resting period. This has the effect of normalizing the absolute amplitude of the signal across the population of test subjects. We then use A as an indicator of the intensity of the motion challenge. We hypothesize that there will be some motion conditions where changes in A are small (A close to 1 meaning the motion intensity is not distinguishable from the resting intensity) with the result that all oximeters can read through the motion with little error. Conversely, we hypothesize that there will be some intensities of motion where A is very large and no oximeters will be able to read accurately. In between, we hypothesize that there are levels of activity that we can "request," which will distinguish between the capable oximeters and those that are not motion tolerant (Figs. 2–4). The range of these levels of A define the motion performance of the oximeter for each type of motion. Error was not defined by the ASTM committee—it was left to the developers to find an acceptable level of error, but generally this meant that the observed accuracy of the oximeter on a motion hand was significantly different from some reference value, typically an oximeter on a stationary hand.

Why do we say a different A for each type of motion? We did not want to make assumptions about the relative difficulty of one type of motion versus

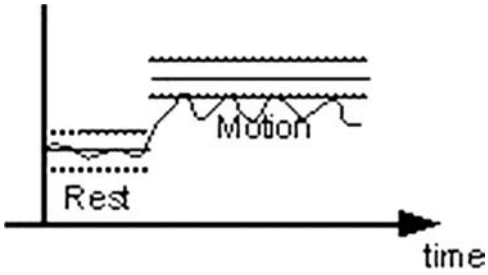

Figure 3. Subject is not exerting sufficient activity to keep the test signal in the desired range. Subject needs to increase their level of activity.

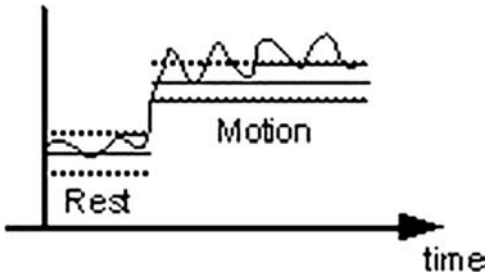

Figure 4. Subject is exerting too much activity causing the test signal to exceed the desired range. Subject needs to decrease their level of activity.

another. One aspect of this research is to determine which motions have independent characteristics, and thus find the minimum set of test motions necessary. We propose that characterizing the time-frequency behavior of the motion signals can give us evidence about the similarities and help reduce the number of test types or identify new test types not yet considered.

Upper and lower control limits (UCL, LCL) specify the upper and lower boundaries for the test signal being fed back to allow a tolerance band around the desired intensity. A 30% tolerance band was chosen. This produced an UCL defined as:

$$\mathrm{UCL} = A \times (1 + 0.3)K_{\mathrm{Ravg}}$$

where K_{Ravg} is defined as the average amplitude (or whatever function we choose) of the resting IR plethysmogram measured immediately before the motion epoch. The LCL is similarly defined as:

$$\mathrm{LCL} = A \times (1 - 0.3)K_{\mathrm{Ravg}}$$

Figure 5 shows an example of the test signal during test as an attempt is being made to keep it within the UCL and LCL, as indicated by the dotted red and white lines.

RESULTS

As our intent was to develop a complete test method, we started with an application (Fig. 14) that made many assumptions. It became evident after only a few subjects that we had no justification for the values we had chosen, nor could we find literature to

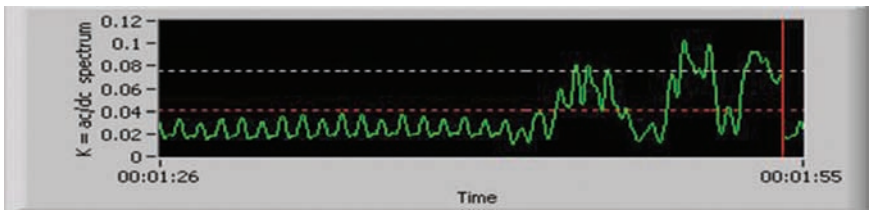

Figure 5. Example of trying to keep the feedback variable within the control limits (indicated by the red and white lines).

support our position. Consultation with manufacturers produced many anecdotal recommendations, but no firm evidence upon which to develop a justifiable test method. We, therefore, began a journey to understand how our system behaved and how to set reasonable values for the parameters of our experiments. This phenomenon, ending with more questions than we started with after each new experimental protocol, repeated itself throughout our studies (and continues). For this reason, much of the work presented is shown empirically, with little group analysis performed, as new questions needed to be answered before the study could be completed. For example, after running our initial application on several subjects, we realized that the factor *A* was not easy to determine. This terminated the study of the motion testing until we could better understand how *A* was related to motion type or position within the test. It was observed that the order of motions, the durations of the periods of rest and motion, how long it takes a subject to recover back to the resting baseline, and how well a subject could keep the test signal within the control limits all needed further examination. We then decided to reexamine some basic assumptions, characterizing the electrical response of the instrumentation system and some basic physiological responses of the subject, so that we could move forward on a sound footing. The gain and position studies are reported to represent these findings.

Test Instrumentation and Data Collection

A method was required to measure the raw plethysmogram in real-time with sufficient resolution to implement our feedback approach. We were fortunate that two pulse oximeter manufacturers, GE/Ohmeda and Philips, make pulse oximeters available, an Ohmeda TruSat® and a Philips M3®, with a real-time raw plethysmographic output. With this equipment available, we have access to the raw IR plethysmogram (60 Hz for the Ohmeda TruSat and about 50 Hz for the Philips M3) and a computed PI at 1 Hz. It would be even more helpful to have access to both the red and IR plethysmograms, but the manufacturers are reticent to provide access to both wavelengths to prevent their calibration curves from being deduced.

The data collected were part of a Duke University IRB-approved study with all volunteers providing appropriate written consent. The Food and Drug Administration also follows a continuing review of the Duke University IRB process. The test uses a control oximeter on the middle finger of one hand to measure the raw plethysmogram and two other DUT on the index and ring fingers of the same hand. The thumb and fifth finger are not used. The saturations measured by the DUTs are compared with an oximeter on the rest hand. Failure is defined as being more than some amount different from the reference on the rest hand (10). This framework makes several important assumptions:

1. Fingers on the same hand see an equivalent motion load
2. Changes in the test variable are a function of the amount of motion and not a function of instrumentation

The first assumption can be tested after each trial, provided that we have appropriate tools. It is proposed to use the time-frequency characteristics of the signal. The second assumption can be validated with studies examining the response of the "system" to differing light-emitting diode (LED) excitation currents and to the position of the hand relative to the heart. We want to ensure that the selected motions impose a change in the test signal more than the changes because of relative position.

Testing and Validating Underlying Assumptions

The proposed method of analyzing the recorded signal from one "reference" finger as an indicator of motion intensity of the other fingers relies on the assumption that the plethysmogram is essentially equivalent for the middle three fingers on the same hand. More precisely, for these three fingers, we postulate the oximeters see a raw plethysmogram with comparable intensity and time-frequency characteristics. This relies on an assumption that the sampled tissue bed interacts linearly with light intensity, and that the feedback variable is independent of the level of the fingers with respect to the heart. The same techniques that we propose to use to explore the independence of the motion types can be used to draw conclusions about the similarity of the finger responses. This is the short-term frequency transform (STFT).

Before beginning to see if our test method would be feasible, we wanted to confirm the sensitivity of our analysis methods and ensure the signal detected was a result of a physiologic change and not an instrumentation gain change in the emitter or receiver circuitry. Confirmation of some basic physiologic responses to position was required to determine if these responses had a larger affect on our signal than the proposed

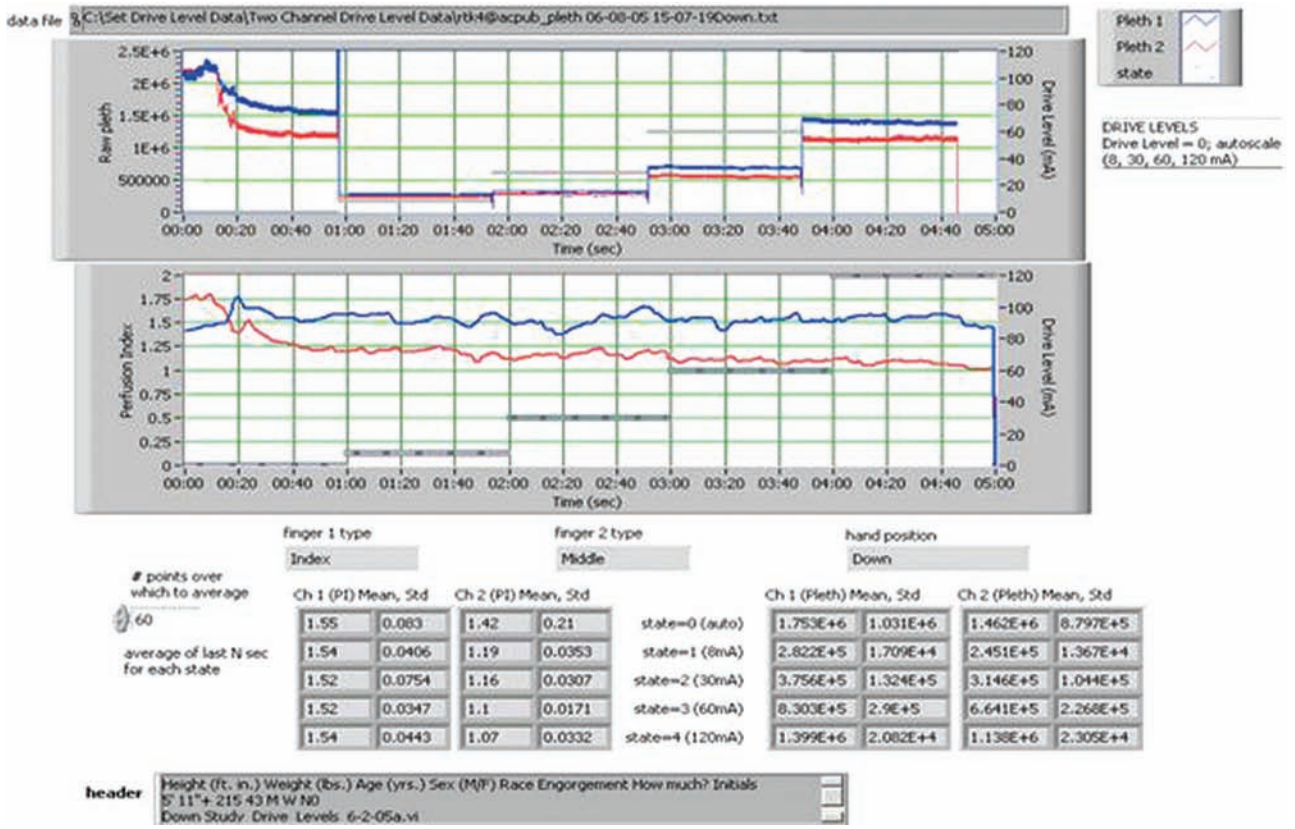

Figure 6. The upper graph show the resting raw infrared plethysmogram (pleth, sampled at approximately 50 Hz) and the lower graph shows the PI (sampled at 1 Hz), for pulse oximeters on two fingers, in this case index and middle, as a function of LED excitation state (auto, 8, 30, 60, 120 mA). The accompanying charts show the mean and standard deviations for each LED excitation state for each channel (60 s average).

motions. Two studies were performed: a gain study and a positional study.

Gain Studies: Response of Test Signal to Differing LED Intensities

With the help of custom software from Ohmeda, we used the TruSats in a mode where the LED emitter outputs could be controlled, thus allowing the transfer functions (output light/input light) to be measured. The subjects were resting with their hands at the level of their heart. The emitter outputs were set at auto-gain (where the oximeter chooses the levels), 8, 30, 60, and 120 mA, and the detected light measured. One study was performed using an opaque bag over only the emitters to determine normal levels of ambient light to distinguish the baseline signal from background electronic noise. The mean and standard deviation for each drive level were compared to see whether the differences in the intensity of the measured raw IR plethysmogram are proportional to the changes in emitter output.

Figure 6 shows an example of the IR plethysmogram and PI as a function of the variation of LED emitter gain as measured using the Ohmeda TruSat oximeter. Ideally, the raw plethsymogram curves should increase linearly, with the 30 mA state generating results 3.75× the 8 mA state. In turn, the 60 mA state should then generate results twice that of 30 mA,

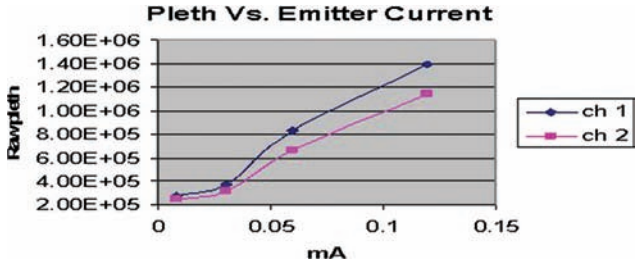

Figure 7. The value of the average plethysmogram versus LED excitation current for the subject in Figure 6 showing a roughly linear relationship for all but the lowest current setting.

and so on. Instead, our experimental data demonstrated only a slight increase in measured light output from 8 to 30 mA. The data from 30 to 120 mA were linear within one significant digit. Additionally, as seen in Figure 6, there is also an unexpected difference in the data from two supposedly identical devices on adjacent fingers. Switching finger–probe-monitor combinations demonstrated that the differences were inherent in the devices but did not affect saturation values.

The linear relationship observed in the plethysmographic amplitudes at the higher excitation currents was as expected but at the lower currents, particularly 8 to 30 mA, the plethysmographic response seemed to

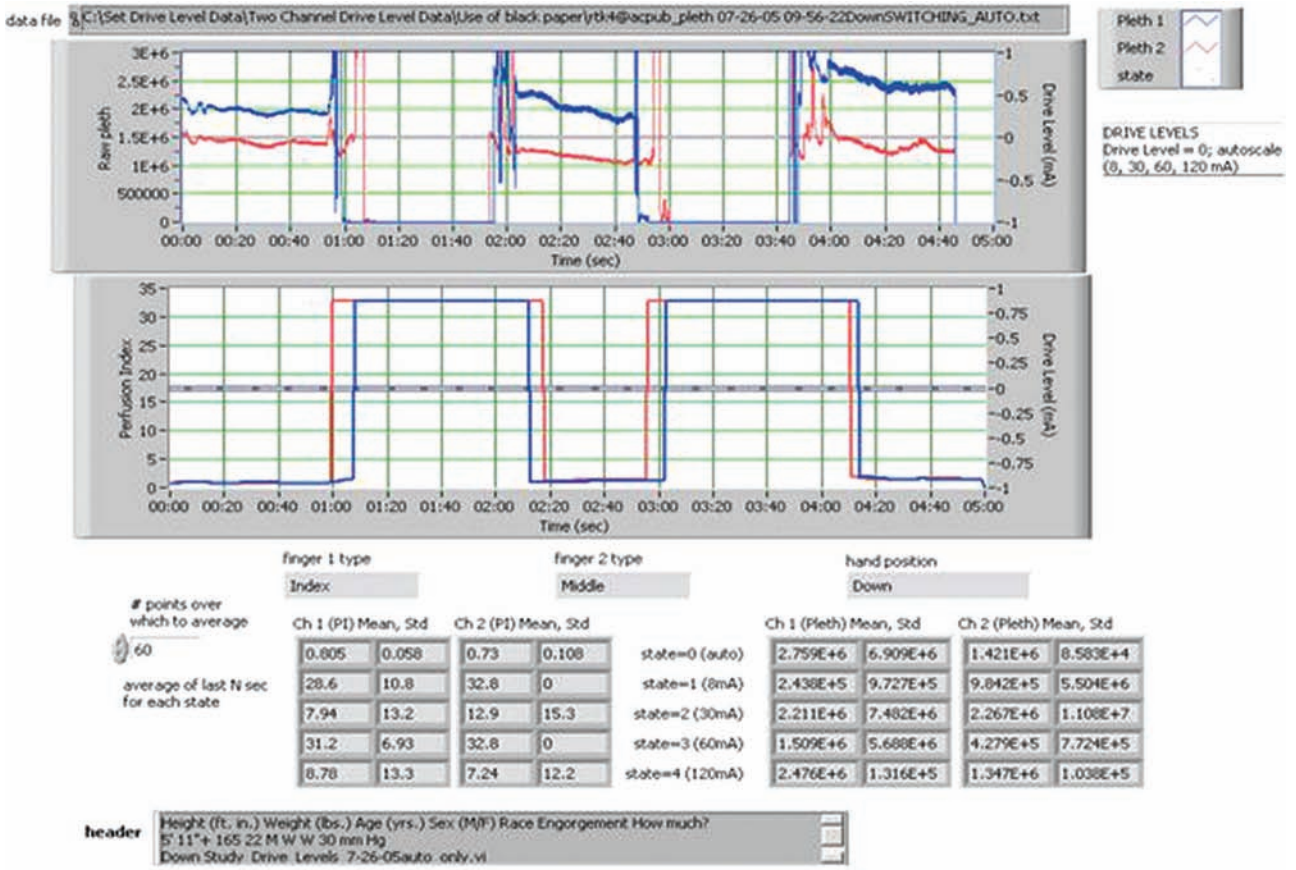

Figure 8. This test explores the background signal by setting the TruSat to auto-gain and applying black tape to the emitter during time 1:00–2:00 and 3:00–4:00 min.

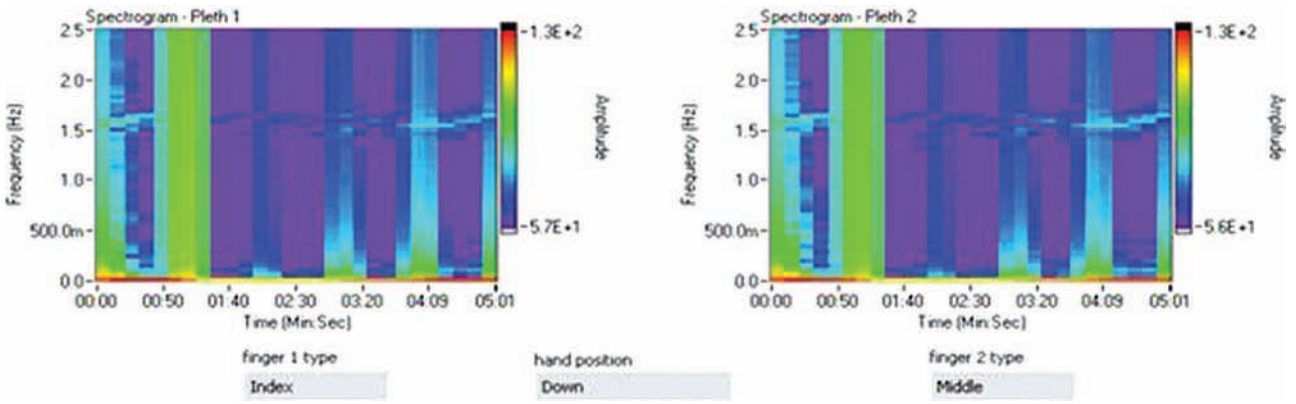

Figure 9. The spectrograms (short-term frequency transform, with a 5-s window) demonstrate that the energy spectra are similar.

lose its linear relationship (Fig. 7). We wanted to know if this was a result of the signal getting lost in the noise floor or the effects of ambient light. An opaque covering was applied over the emitters to determine the background signal on the detectors. The covering was intermittently removed and replaced during this test, and the results are illustrated in Figure 8. The background signal with no LED illumination is effectively zero, excluding ambient light as the cause of the nonlinearity.

A STFT frequency analysis was performed of the data in Figure 6, with spectrograms displayed in Figure 9, to demonstrate that the signals seen by two adjacent fingers were equivalent. The curves look so similar when compared visually that no additional computation was used.

There is a jump in the plethysmogram when the TruSat emitters were set to 8 mA from their initial auto-gain setting, thought to be because of the settling in the receiver circuitry. As the emitter gain is then increased, the spectrograms are observed to increase in amplitude, consistent with the increase in emitter drive current. At this juncture, we are unable to precisely determine why the 8 mA emitter setting

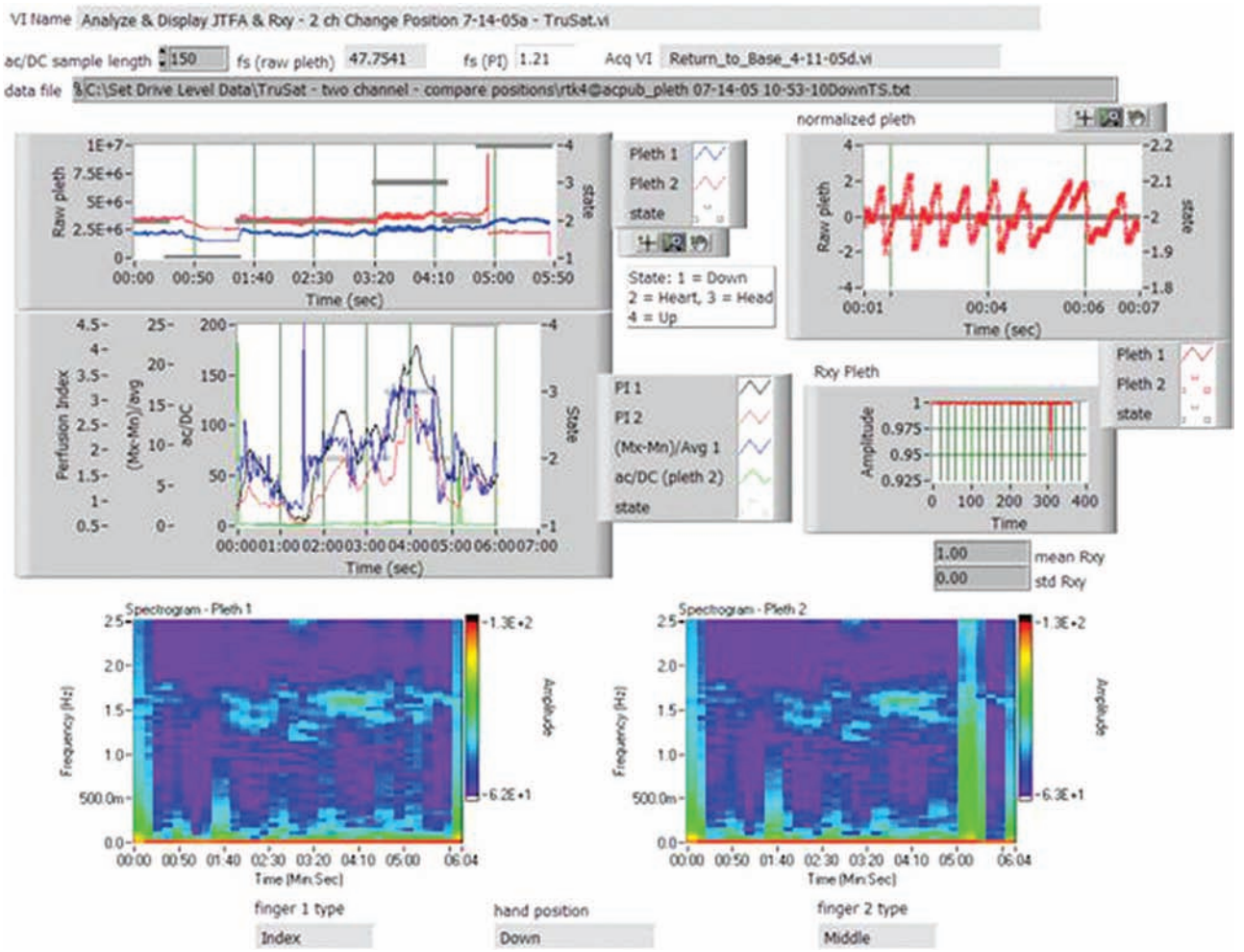

Figure 10. Tool developed in LabVIEW to explore the characteristics of plethysmogram signals on the same hand (not including thumb and pinky).

causes this response, with the most likely theory being the possibility of an inherent nonlinearity in the response of the emitter diodes.

Positional Studies: Response of Test Signal to Varying Hand Position

Are the effects on our test signal of changing hand position larger than the effects we see with some of our exemplar motion types? Varying the position of the finger/probe with respect to the level of the heart provided some interesting data to address this issue. The protocol to investigate positional impact used the PI as calculated by the TruSat or M3 as a function of arm position (down, heart level, head level, up/raised). Position started at heart level and stepped through the following states: down, heart, head, up. After each state, the hand was returned to the heart position as a reference. To simplify our experimental setup, we used the same pulse oximeter on the middle finger to provide the raw IR plethysmogram. This is our control oximeter. The ring and index fingers then provide platforms for testing two additional devices. All the position and drive level studies used dual TruSat oximeters. Additional positional studies used two Philips M3 oximeters to confirm observations made with the TruSats.

The raw IR plethysmogram displayed an increasing trend with amplitude as the hand position was elevated higher toward head level with a concomitant increase in PI, apparently because of the larger AC component of the pulse, but seemed to decrease when the position was raised above the head. A sample of this response is seen in Figure 10. The upper left curve shows the raw plethysmogram acquired from a pair of Ohmeda TruSats as a function of hand position with respect to the heart (referred to as the state). The curve underneath this shows the PI as calculated by the TruSats and two prospective test signals, (max − min)/avg and AC/DC, again as a function of the position. The curve in the upper right shows a 7-s period comparing the time domain wave forms from the index and middle fingers. The curve underneath this shows the correlation between the two plethysmograms as a function of time. Underneath these curves are the two spectrograms (STFT). This response is found in both the TruSats and the M3s, but not consistently with all subjects. Both a normalized correlation coefficient calculation and the

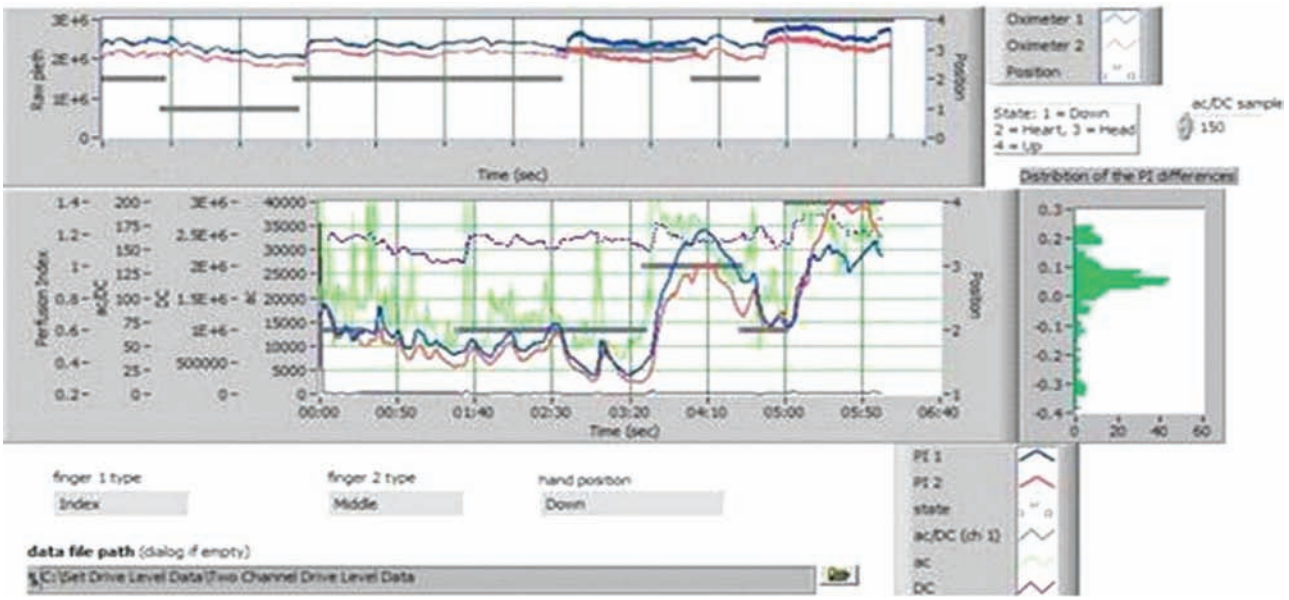

Figure 11. The recorded raw plethysmogram is split into its AC and DC components using an Fourier transform based analysis calculated over a 3-s interval. Notice that the DC component (purple) is much less dependent on the position than the AC component (bright green).

STFT spectrogram shown in Figure 10 indicate that the two oximeters on the same hand were seeing the same magnitude of activity in the IR plethysmogram.

For some subjects, the PI "followed" the hand position, increasing as the hand was raised, as shown in Figure 11.

The middle graph of Figure 11 demonstrates how the AC and DC components respond to the changes in position. From these curves, it appears that the change in the AC component is the greatest contributor to changes in PI (as measured by the TruSat), indicating that our test signal should focus on the AC characteristics. The TruSat oximeters continued to exhibit a small bias between the two monitors shown by the offset between the two signal curves in the top plot of Figure 11 but, importantly, the devices did not demonstrate an appreciable difference in measured saturation.

We continued to explore the question of how similar the finger plethysmograms are by comparing the wideband plethysmograms (the raw signal compensated for by the gain of the LEDs and the photodetector amplifier) from two fingers on the same hand. For both the TruSat and M3s, the motion generated with both fingers was synchronous, via visual assessment of an equivalent spectrogram. Figure 12, performed using the M3s, shows that, for noisy plethysmograms, the STFT is useful for comparing equivalency and that both [max − min]/avg (blue signal in the second trace) and AC/DC (green signal in the second trace) track perfusion though each can be quite noisy. Importantly, we were able to determine when the two fingers did not move synchronously, as can be seen by comparing the spectrogram in Figure 13.

DISCUSSION

We need to understand our instrumentation and the system that we were exploiting, namely the response of the tissue finger bed to light. It is important to be certain that the changes being measured were from the added motion and not from changes in underlying perfusion, possibly as a result of a change in position with respect to the heart, or a nonlinearity. Although much of what we seek is likely known to corporate research labs and anecdotally, we could not find published evidence of how the tissue bed responds to varying intensity exposure, nor could we find information about the plethysmographic response with respect to position for our particular instrumentation configuration. Rather than make assumptions, several simple experiments were devised to characterize our systems' performance. Two basic experiments were performed: 1) we exposed the tissue bed to a known intensity excitation holding the position constant, and 2) we varied the position of the hand and observed the response. In each of these experiments, we explored whether fingers on the same hand had equivalent plethysmograms, because our proposed test method uses one finger to control the amount of motion on the other two fingers. The visual representation of the STFT was used to compare finger responses with a more elaborate method for assessing similarity, based on the average difference of the point values under development.

In parallel with the continuing basic studies above, we developed an application to prototype a potential test method. Our application allows us to select the order of motions, the duration of the rest and motion

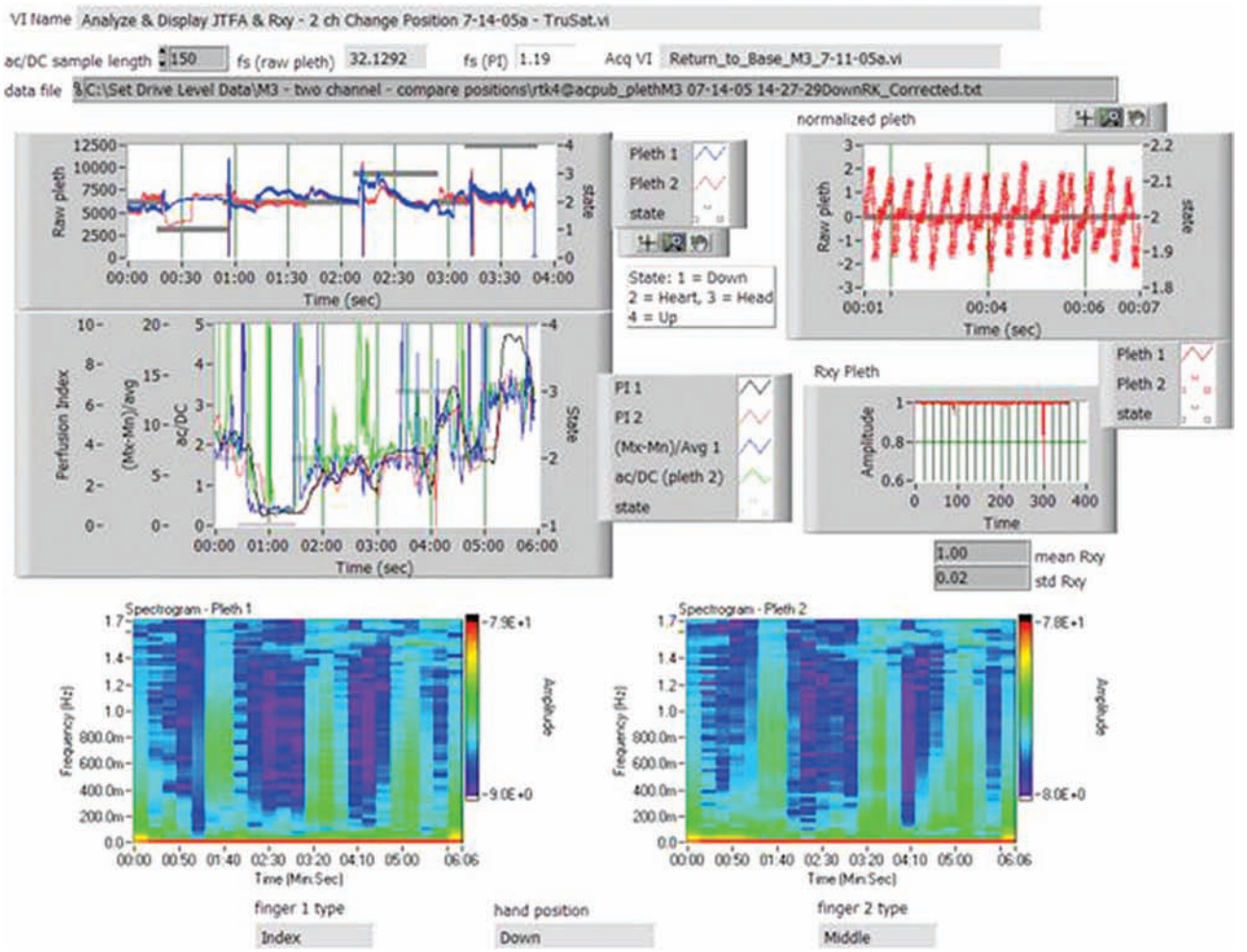

Figure 12. Same as Figure 10 but using the Philips M3. Notice the amplitude of the plethysmogram is 100× smaller than for the TruSats. We were unable to obtain the gain corrected plethysmogram values for the M3 but the signals were adequate for our studies anyway.

periods, the desired *A*, and the desired control limits. We exercised this application on several volunteers, which raised several questions:

- Does the type of motion that proceeds affect the results? Would the subject fatigue for one type of motion and not another and would this influence the subject's ability to keep the signal within the control limits?
- Does the order of motion types influence the results?
- Might exercise lead to exhaustion and the inability to maintain a high intensity state (not reach the control limits)?
- Does the baseline recover to the same (resting) level? Which is the correct resting baseline to use in the calculation of *A*: the initial resting period, or the period immediately preceding the motion?

Figure 14 illustrates an example of the LabVIEW® based data collection system. Set-up parameters include length of rest period, length of motion period, the computation to be preformed on the raw plethysmogram (if any), and the control limits for that study. The subject performs the indicated motion, varying the intensity to attempt to maintain the computed feedback variable, *K*, within the range indicated by the control limits. The screen shot shows the data transition from a rest period to a motion period.

Where Do We Go from Here?

We have demonstrated the tools needed to scientifically and systematically create a motion standard for pulse oximetry. The next step will be selecting values for the parameters, using them to collect data from a representative population of subjects, and developing statistically significant conclusions. By creating a closed-loop control system, it is hoped that testing can be reproducible and will allow devices to be compared using an equivalently challenging test. To accomplish our test method, it was necessary to determine if the plethysmograms are equivalent in the fingers on the same hand, and that the signal observed is a result of the added motion and not an artifact of our measurement system, including the instrumentation and the human subject.

Some work is left to be done to select the computation of *K*, such that most subjects will be able to keep the test signal within the control limits. The

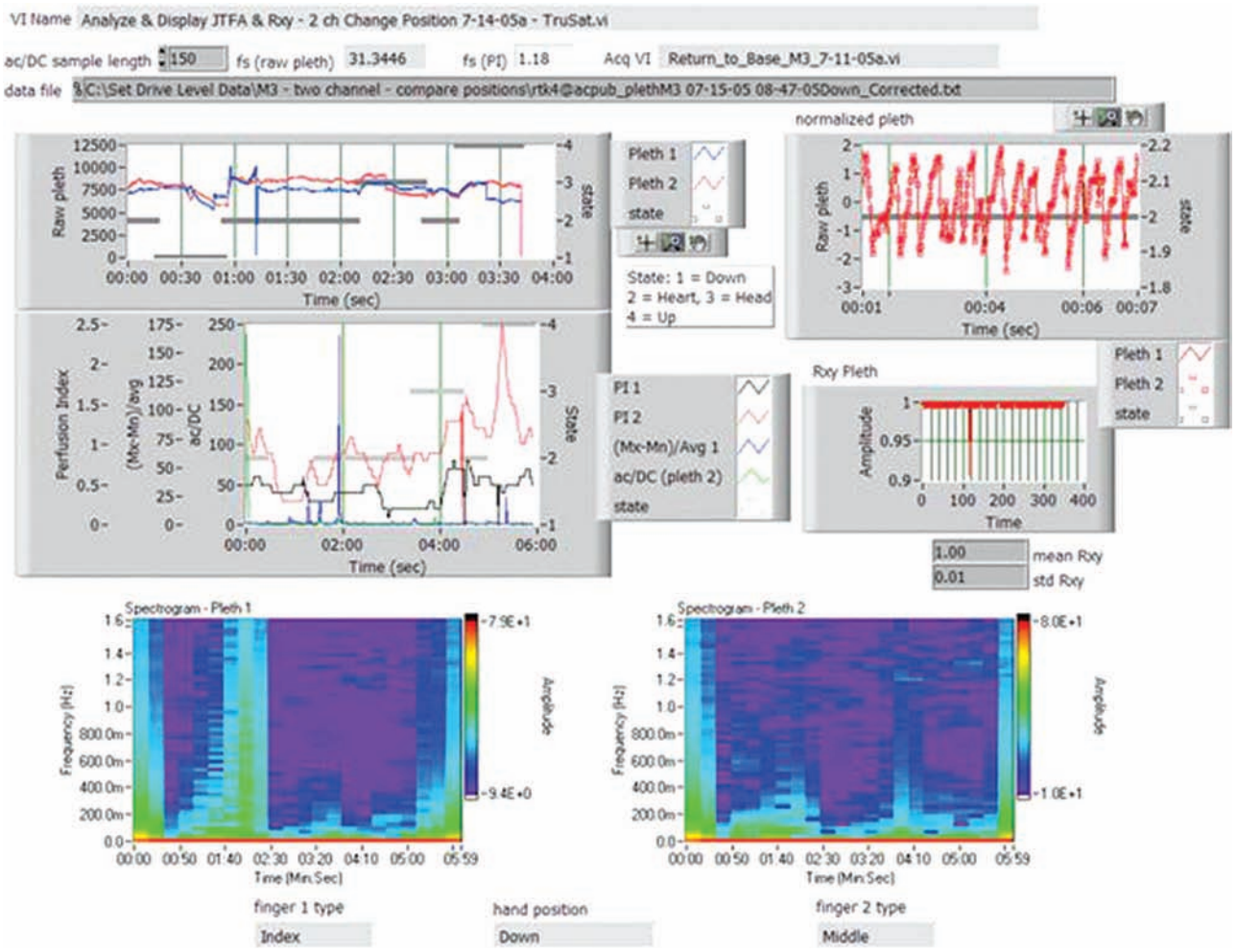

Figure 13. Data collected using the Philips M3. These fingers are not presenting the same motion challenge. Differences can be seen in the raw plethysmograms and the short-term frequency transforms. Even the correlation function has more noise than usual.

ability of a subject to keep within the control limits is a function of how fast the system responds and the formulation of *K*. Our system could redraw the screen once per second, leading to a less than smooth feedback signal. Using a longer averaging filter or more points in the calculation will create a feedback variable that reacts more slowly. We instituted the concept of %IN, defined as a measure of time within the control limits compared with the time outside the control limits, when it was realized that many novice subjects had difficulty keeping their test signal within the desired range and it seemed the more experienced subjects had less difficulty. The degree to which the subject can keep the test signal within the control limits may be crucial to demonstrating the feasibility of this method. An acceptable value needs to be found, likely by experimentation and iteration.

Whether there is a critical threshold on %IN, below which the test becomes invalid, remains to be seen and is the focus of future work. It is expected from prior observations that training will improve the attainable %IN, and that %IN will also vary between motion types, as some motions are more difficult to maintain than others. We may use %IN as a quality control measure to discard invalid tests, just as the STFT may identify when the fingers are not acting in synchrony.

Proposed Protocol

Our proposed protocol will have the subject perform the motion for several increasing values of *A*. Preliminary experiments have shown us that A may not be the same value for all motions. An initial value of A will be set, and the subject will be asked to keep the amplitude of the generated test signal within the UCLs and LCLs for as much of the motion period as possible. At some point, the amount of motion generated with increasing *A* will cause failure (A_f) of the tested device compared with the reference oximeter on the stationary hand. Barker and Shah (8) used the concept of percentage of time when the oximeter error exceeded a specified threshold. As additional subjects are tested for that same motion, additional values for A_f will be determined. It remains to be seen how A_f behaves over a population of subjects and whether it is reproducible for a subject and across subjects. With these data in hand, a fair threshold for a "pass" or

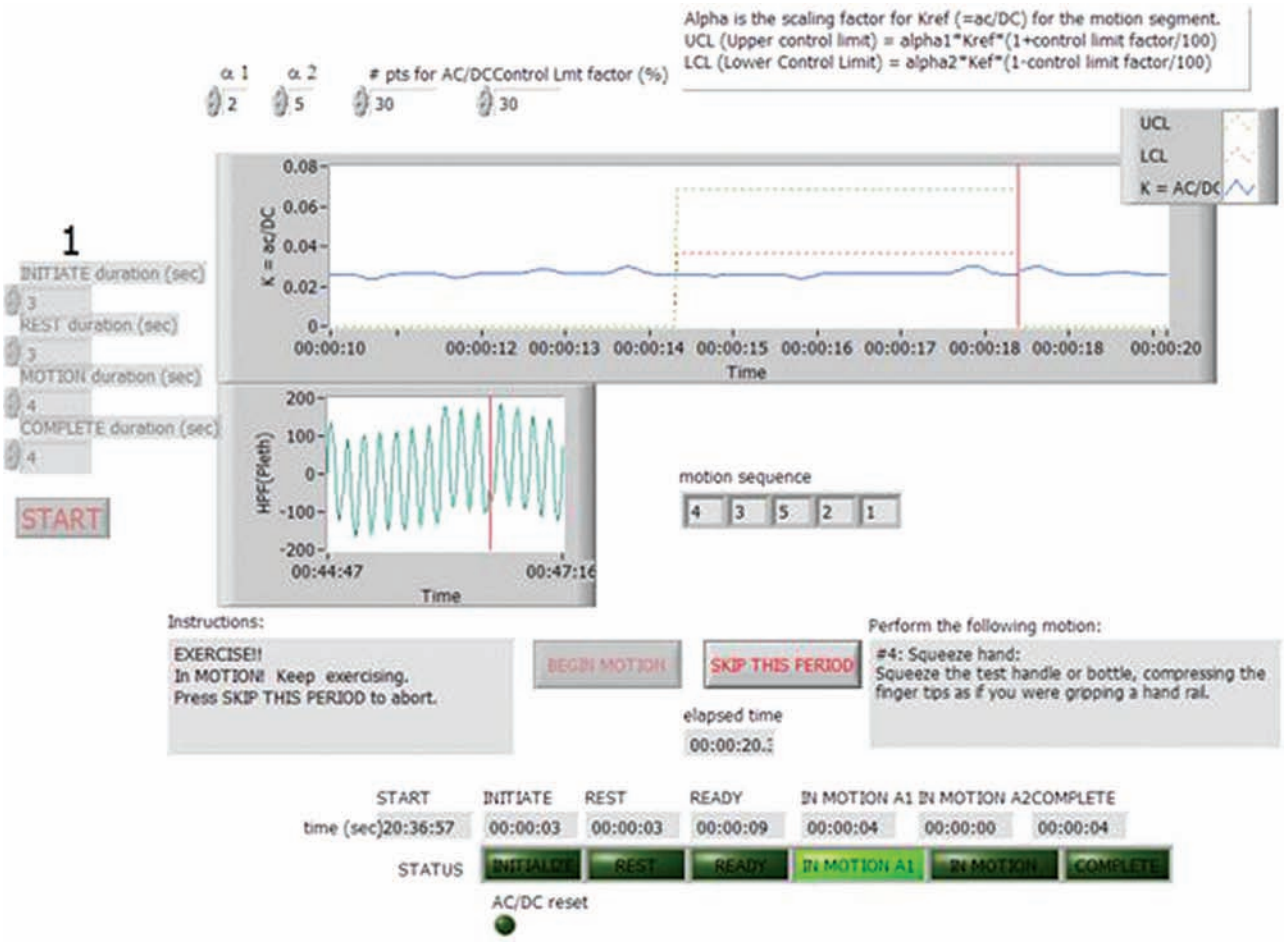

Figure 14. LabVIEW® screenshot of a data collection program designed to include the human user in the feedback loop. The motion sequence, duration of each period, and control limit parameters are configurable. Directions are given to the operator and subject. Program name: Motion Characterization 12-10-2003.vi.

Table 1. Proposed Testing Grid

	Motion type				
Monitor	Flexing or waving	Scratching or rubbing	Flexion-extension	Squeezing	Tapping
A	$A_f = 3$	$A_f = 2.5$	$A_f = 4$	$A_f = 2$	$A_f = 4$
B					
C					

"fail" can be determined. It is expected that some devices will have more difficulty with some motions than others, but a certain minimal level of performance should be mandatory to describe a device as "motion-resistant" or equivalent.

One concept for reporting the performance of each oximeter is a table format with the error measured as a function of motion type (Table 1).

Finally, the relative amplitudes and shapes in the STFT spectrograms we believe to be the motion signatures. We postulate that two motions with similar spectrogram signals are not independent, only one is needed in the test method. One of the next dilemmas needing to be addressed is how to validate this postulate. This will allow us to produce an efficient test, one that has a minimum amount of testing yet is still effective in differentiating motion-resistant oximeters from nonresistant ones.

CONCLUSIONS

We have proposed a method and rationale to perform motion testing that we believe will be reproducible and robust with respect to comparing motion-resistant pulse oximeter designs. Tools have been developed to explore and test the validity of the underlying assumptions, including the reliance on adjacent fingers seeing equivalent motion challenges and the independence of motion types. We believe we have identified variables that may have an influence on the ability of the test to be effective. What is left to be done is to perform rigorous, statistically valid

protocols to select an appropriate form of the test statistic, optimize the duration of the resting and testing periods, and order the motions in an appropriate way. Our observations have demonstrated that the best chance for success relies on using trained volunteer subjects that can consistently control their motion and the resulting plethysmograms. Toward this end, we will seek additional opportunities to bring our agenda to completion. This work is just beginning.

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The Effect of Motion on Pulse Oximetry and Its Clinical Significance

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Pulse oximetry is an important diagnostic and patient monitoring tool. However, motion can induce considerable error into pulse oximetry accuracy, resulting in loss of data, inaccurate readings, and false alarms. We will discuss how motion artifact affects pulse oximetry accuracy, the clinical consequences of motion artifact, and the methods used by various technologies to minimize the impact of the motion noise.
(Anesth Analg 2007;105:S78–84)

Pulse oximetry is an important diagnostic and patient monitoring tool widely used throughout the hospital environment. Although pulse oximetry is highly reliable when used on motionless and well-perfused patients, anything that affects the detection or processing of the biological signals on which it depends can affect the accuracy. Numerous factors have been shown to negatively affect the absorbance characteristics or signal-to-noise ratio of pulse oximetry. Factors affecting the absorbance characteristics include dyshemoglobins (carboxyhemoglobin and methemoglobin), dark skin pigmentation, nail polish, and dyes (1–7). A low signal-to-noise ratio leading to inaccurate readings can be caused by a low pulsatile signal (low perfusion), high noise (bright lights, electromagnetic interference, or motion), or a combination of the two (such as motion occurring during low perfusion) (5–12). Of all of these factors, motion artifact has been the most clinically troublesome, resulting in loss of data, inaccurate readings, and false alarms (5–7,9,11). Voluntary and involuntary movement, such as movement during transport, tapping, rubbing, scratching, waving, shivering, and seizures in adult and pediatric patients; and kicking, stretching, crying, flexing, and imposed motion in neonates, are some common sources of patient motion in the clinical setting (13, and see footnote[1]). Motion artifact can either cause the pulse oximeter to interpret motion as the true signal or obscure the true signal with noise, leading to inaccurate readings, false alarms, and most importantly, missed true alarms. Problems with pulse oximetry reliability, in turn, can result in an increase in caregiver workload, stress, and need for patient handling, all of which can lead to decreased patient safety and increased cost of care (14–17). Various methods have been used to attempt to minimize the impact of the motion noise, all for false-alarm management, including, most recently, algorithm-based motion rejection methods.

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[1]Masimo's clinical data set contains data for over 1000 patients from all clinical areas.

PRINCIPLES OF OXIMETRY

To understand how patient motion affects the accuracy and reliability of pulse oximetry, one must first understand the general principles of the technology. Takuo Aoyagi, the inventor of pulse oximetry, based his original technology on two physical principles: 1) the light absorbance of oxygenated hemoglobin is different from that of reduced hemoglobin at the two wavelengths used in pulse oximetry (red and infrared) and; 2) the absorbances at both wavelengths have a pulsatile, or oscillating (AC) component, which is the result of the volume change, normally from arterial blood, occurring between the emitter and the detector of the sensor (18). This volume change is most commonly due to pulsations from the cardiac cycle. There is also a nonpulsatile, or stable, component (DC) that results from light attenuated by skin, fingernails, tissue, bone, and static (or nonpulsating) blood. This nonpulsating blood is composed of variable amounts of arterial, venous, and capillary blood. All pulse oximeters have been empirically calibrated by desaturating healthy volunteers in an oxyhemoglobin range of 100% to 70%. By measuring oxyhemoglobin at numerous stable points within this range, a calibration curve can be generated by collecting absorption data for both the red and infrared wavelengths. These raw data are converted to a "ratio of ratios" (r) (Eq. 1), which is then associated with a specific SaO_2 reading during the desaturation. For any computed r, therefore, there is an associated, estimated SaO_2 reading from the calibration curve. The measurement of SaO_2 by two-wavelength pulse oximetry has been termed Spo_2 (19).

$$r = (AC_r/DC_r)/(AC_{ir}/DC_{ir}) \quad (1)$$

BASIC ASSUMPTIONS IN PULSE OXIMETRY

This empirically calibrated pulse oximeter is highly accurate when these basic assumptions are met:

1. All the hemoglobin present is either oxyhemoglobin or reduced hemoglobin.
2. There are no other absorbers between the emitter and detector other than those present during the empirical calibration.
   a. The absorption characteristics of these "other absorbers" are the same as during the empirical calibration.
3. All the blood that "pulsates" is arterial blood.

As mentioned above, there are numerous factors that alter these assumptions, and therefore will decrease the accuracy of the device. The effects of most of these factors have been adequately described elsewhere (2–12). Here, we examine in more detail, the effect of motion on the accuracy of pulse oximetry.

EFFECTS OF MOTION ON PULSE OXIMETRY READINGS

Motion can induce considerable error into pulse oximetry accuracy. The mechanism of this has been poorly understood. Before the invention of read-through motion pulse oximetry, conventional wisdom was that motion was transmitted to the sensor introducing noise equally to both the red and infrared components of the signal, thus obscuring the biological signal. Some investigators even considered the forces required to dislodge the pulse oximetry sensor from the digit. Langton and Hanning, for example, correlated the force required to displace the sensor with the degree of motion-induced artifact (20). According to this theory, the motion-induced noise affected both the red and infrared wavelengths, and when the amplitude of the motion noise was large enough, it obscured the biological signal. The motion noise, therefore, resulted in an *r* ratio of approximately one, which corresponded to a saturation value between 82% and 85% in the empirical calibration curve (21,22). The problem with this theory is that false desaturations below 50% were commonly observed. It was eventually theorized that patient motion can cause movement of the venous blood, as well as other normally nonpulsatile components (such as tissue fluid in edematous patients), along with the arterial blood (21–24). The pulsatile components (AC components) of the signal, then, are composed of more than just arterial blood, which may lead to falsely low saturation readings (due to lower venous saturation). If motion is combined with low perfusion at the sensor site, then the venous blood makes a more significant contribution to the pulsatile component and drives the Spo_2 reading even lower. Low perfusion is common in critically ill neonatal, pediatric, and adult patients, all of whom require accurate, continuous oxygenation monitoring. Low perfusion in the patient can corrupt the Spo_2 reading in three ways: First, with low perfusion there is an increase in the ratio of venous blood to arterial blood at the measuring site. Second, the decreased perfusion results in increased oxygen extraction and, ultimately, a lower venous saturation. Third, the lower perfusion level is associated with a lower pulse amplitude or AC component, so the noise of motion can have a greater effect when combined with a small biologic signal. Therefore, small amounts of motion will cause the Spo_2 to be composed of a larger venous component with a lower venous saturation resulting in lower Spo_2 values.

CLINICAL IMPACT OF MOTION ON CONVENTIONAL OXIMETRY

Motion artifact can reduce the perceived clinical significance of pulse oximetry alarms by causing false alarms and data dropouts when the signal processing is overwhelmed by the motion noise. This "Cry Wolf" phenomenon was shown in a study designed to test the clinical significance of patient monitoring alarms in the pediatric intensive care unit (PICU). Lawless found that of the 957 pulse oximetry alarms that occurred in a 3-day trial period, 71% were false and only 7% were clinically significant (16). In another study conducted on 123 patients recovering from general or regional anesthesia, Wiklund et al. (25) found that of the 1516 pulse oximeter alarms during the 207 h of observation, only 23% were true. Fletcher et al. (26) found that in a group of preterm and term infants, motion artifact was present in all infant studies, comprising 19% of the monitored time during quiet sleep, 49% of active sleep, 49% of indeterminate sleep, and 91% of the time during wakefulness. In addition to affecting Spo_2 measurements, motion artifact has been shown to affect the heart rate measurement by pulse oximetry as well. Barrington et al. (27) demonstrated in the neonatal intensive care unit (NICU) that the heart rate parameter was in error (error $>$10 bpm) as much as 25% to 29% of the time, and that this error was specifically related to the patient's movement of the extremities. The false alarms and loss of data that occur with motion artifact can have the effect of increasing caregiver workload by requiring them to repeatedly and needlessly check on the patient and the equipment. Understandably, this can cause caregivers to distrust the significance of the alarms, and may result in alarms being ignored or even turned off (16,28–30). Thus, motion artifact can significantly reduce the value of pulse oximetry as a tool to help clinicians maintain vigilance over their critically ill patients.

COLLECTING AND CHARACTERIZING MOTION DATA

In an effort to characterize the types of motion, which lead to oximetry errors for algorithm development, Tobin et al. (13) at Datex-Ohmeda (Louisville, CO) collected 14.5 h of data on 35 patients who

exhibited motion in the different critical care areas of the hospital including the intensive care unit, PICU, NICU, operating room, and ambulance. They found that, although a wide range of motion types led to oximetry error, most errors were generated by intense, aperiodic, random movements that lasted 30 s or less. However, in approximately 5% of the cases, motion exceeded 1 min. Infant patients demonstrated these types of motion more than adults and, in fact, were much more likely to be observed moving compared with adult patients (31% compared with 7%, respectively). Masimo's clinical research data collection set, which includes thousands of hours of data collected from more than 1000 patients in all clinical areas, is consistent with these findings, showing that patient motion tends to be composed of discrete, aperiodic episodes occurring closely together, so that their effect on pulse oximetry would appear as continuous motion, often lasting more than several minutes at a time. In addition, the Masimo clinical data set contains numerous files of continuous motion exceeding 30 min such as shivering patients and those with imposed motion during ground or air transport. Therefore, motion-resistant pulse oximetry has to be able to work during short periods of motion, as well as for long continuous periods of both aperiodic and periodic motion.

Solutions to the Noise Problem

As previously discussed, continuous monitoring with pulse oximetry is necessary for all acute care patients, but use of conventional oximetry often results in too many false alarms, diminishing its predictive value and impairing patient safety by distracting caregivers. In order for pulse oximetry to be more help than hindrance to the health care provider, the motion artifact problem needed to be improved. Medical device engineers have used various techniques to address motion artifact in pulse oximetry. Commonly used strategies include averaging the saturation data over a longer period of time, holding data until clean data are qualified, then averaging that with the previous clean data and implementing alarm delays. Additionally, with the advent of read-through motion and other kinds of motion-resistant technologies, sophisticated algorithms, some using parallel processing with multiple algorithms, have been used to isolate the biological signal in the presence of noise.

Data Averaging, Alarm Delay, and Holding Data

Technologies that smooth data with longer averaging algorithms to reduce the effect of motion artifact can result in fewer false alarms. Figure 1 demonstrates the theoretic effect of increasing averaging time. Rheineck-Leyssius and Kalkman tested the effect of data averaging on false-alarm rates in a study conducted on 200 postsurgical patients (31). Spo_2 values for each patient were recorded with a laptop computer, and then analyzed to identify episodes of low

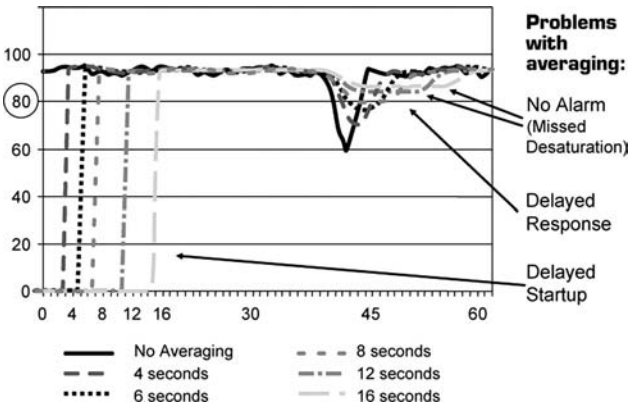

Figure 1. Increasing averaging delays onset of readings and smoothes data displayed.

Spo_2 and motion artifact. The data were then subjected to an algorithm that simulated data averaging settings of nine different durations between 10 and 90 s. The study found that, when Spo_2 values were subjected to 10 s averaging (default 3 s averaging), alarms were reduced by almost 50%. When the data were averaged for 42 s, the alarm rate was reduced further by 82%, but 6 of the 73 true severe hypoxemic episodes were not detected. In a more recent study, designed to compare the sensitivity and specificity of several pulse oximetry technologies during motion and low perfusion, Barker found that technologies that had longer default averaging times of 10 and 12 s had a decreased ability to detect rapidly occurring hypoxemias, compared with those with 5 to 8 s averaging (32). Data averaging, therefore, has two effects: first, it increases the amount of time needed to report an initial value. Second, it has the effect of smoothing any resultant changes in oxyhemoglobin saturation, which, in turn, can directly impact the diagnosis and treatment of patients. The diagnosis of obstructive sleep apnea (OSA), for example, is dependent on the tracking of transient desaturations in the patient. Figure 2 shows data from an infant diagnosed with OSA of prematurity. Frequent OSA episodes result in rapid transient desaturations, the magnitudes of which are clearly detected when the pulse oximeter is set for 2-s averaging. These transient desaturations are almost completely lost when the device is set for 16-s averaging.

Rheineck-Leyssius and Kalkman formally investigated the effect of eliminating alarms for transient episodes of low Spo_2 readings by introducing a delay between the onset of the alarm condition (a reading of $<90\%$ Spo_2) and the triggering of the alarm. This time delay strategy was compared with the effect of decreasing the alarm condition to 85% to determine which was more effective at eliminating false alarms. The researchers found that decreasing the alarm threshold from 90% to 85% would eliminate the same number of false alarms as delaying the triggering of the alarm 15 s from alarm condition onset (31). However, the incidence of hypoxemias lasting longer than

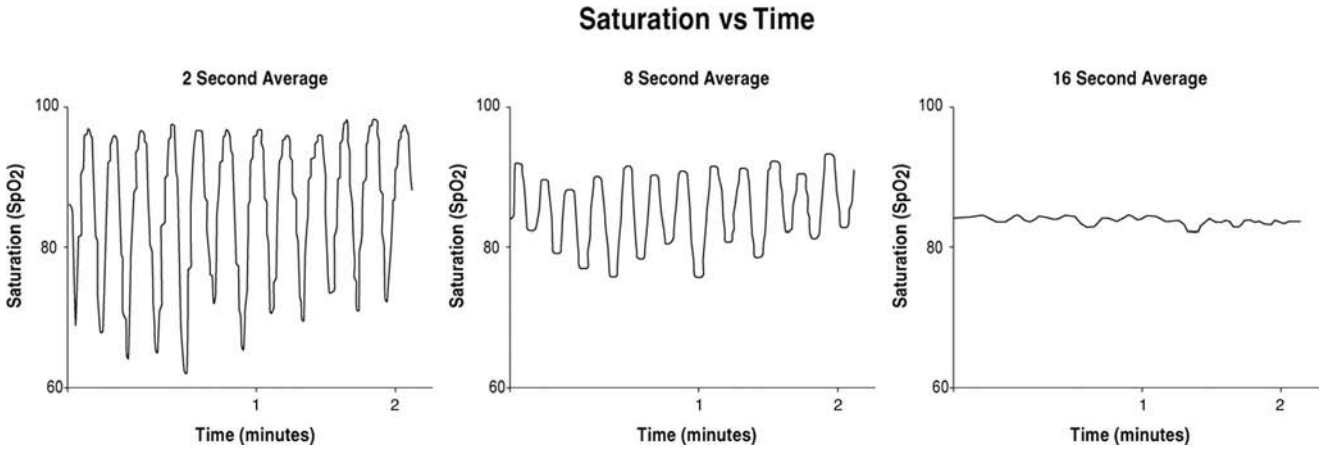

Figure 2. Data from an infant diagnosed with apnea of prematurity. Frequent apneas result in rapid transient desaturations, the magnitudes of which are clearly detected when the pulse oximeter is set for 2-s averaging. Transient desaturations are almost completely lost when the device set in 16-s averaging.

1 min in patients for whom the alarm threshold was set at 85% was higher than in patients for whom the alarm threshold was set at 90%, suggesting that the time delay strategy was the safer method of reducing false alarms. Neither method, however, provides a safety net for patients suffering from rapid desaturations. Poets and Southall found that preterm infants can desaturate at a rate of up 12.6% per second (33). Thus, an alarm delay of even 15 s could prevent a patient from receiving time-critical, lifesaving intervention.

Manufacturers have also used data holding strategies to decrease false alarms. With this technique, pulses are qualified, and only those fitting certain criteria are used in the calculation of Spo_2. When motion is sufficient to affect the Spo_2 reading, the current Spo_2 is displayed until new clean data are qualified and added to the previous buffer of good data. The holding of data may continue for up to 50 s if good data are not found (34). This technique has been shown to miss significant desaturations in both volunteer motion studies and clinical studies (32, 35,36). By using pulse oximeters that use any of these strategies, clinicians are left to pay for the reduction in false alarms at the cost of lost information on their patients' oxygenation status. It is important to note that current International Organization for Standardization (ISO) standards for pulse oximeters require data to be updated at least every 30 s (37).

Read-Through Motion and Motion Tolerant Algorithms

Several manufacturers of pulse oximetry systems reference the use of algorithms that are motion tolerant in their marketing literature. Because these algorithms are highly proprietary, the details on how each manufacturer's technology identifies and processes the incoming signals are generally not available. Signal-processing algorithms for conventional pulse oximeters were typically time-domain based, using analog filtering and moving average techniques to identify and process biological signals (4,23,24). Masimo SET, a technology that reads through motion, uses several signal processing techniques. Masimo's proprietary Discrete Saturation Transform (DST), one of the several algorithms used in Masimo SET, is an example of a time domain algorithm. The DST algorithm was developed specifically to identify the arterial signal in the presence of the nonarterial (venous) signal that occurs during motion (22,23,38,39). The DST comprises a reference signal generator, an adaptive filter and a peak picker, which work in concert to determine the most likely Spo_2 value based on the incoming signals. The reference signal generator uses a combination of the red to infrared ratios and the detected signals to produce a series of noise reference signals. The noise reference signals (serially from 0% to 100% Spo_2) are then compared with the incoming signal using an adaptive filter. A power spectrum is created by plotting the power output as a function of Spo_2, from 0% to 100%. The right-most peak (identified by the peak picker) of the power spectrum plot during motion corresponds to the highest saturation value, which should be the arterial saturation, because arterial saturation is higher than venous saturation. During nonmotion conditions, there is only one peak. The output of one or more of the other algorithms may also be evaluated by a confidence-based arbitrator algorithm, which produces a measure of confidence about the quality of the incoming data.

Philips' FAST Spo_2 (Fourier Artifact Suppression Technology) is a technology that makes motion-tolerant claims and depends on a frequency-based algorithm (40). According to a published description, the FAST-Spo_2, algorithm first identifies the frequency components of the pulse rate and compares those to the frequency components of the incoming signal to select the component that is at the pulse rate for both the red and infrared wavelengths. This component, or value, is then used to calculate the oxygen saturation after several additional "checks" are made. These include determining if the frequency components are multiples of the selected pulse rate, if there is a good

correlation between the red and infrared spectra at the selected frequency and if the calculated Spo_2 value is reasonable and close to the last three accepted values (41). Nellcor's Oximax N-600, on the other hand, which uses the "Variable Cardiac Gated Averaging" algorithm, appears to be time-domain-based, in that it attenuates incoming signals that do not occur synchronously with the average rhythm of the pulse rate and allows the parts of the waveform that are synchronous with the heart rate to remain unattenuated and thus contribute more to the calculated Spo_2 (42).

Evaluation of Motion-Resistant Pulse Oximetry Technologies

There are many published studies comparing the performance of motion-resistant pulse oximetry technologies to conventional technologies and to each other. These studies can be categorized into three types; 1) those conducted in a laboratory setting on healthy volunteers, 2) clinical studies of hospitalized adults, pediatric, or neonatal patients usually in intensive care units, and 3) OSA studies.

Laboratory studies tend to use either "hand motion machines" or depend on subject-generated motion. Protocols that use machine-generated motion have the advantage of testing devices with standardized, highly consistent, and reproducible motions. The pros and cons of testing devices with subject-generated versus machine-generated motion have been debated (43–46). Some researchers have studied tapping and rubbing motions using both techniques and found there to be little or no differences in the results (46–48). All laboratory studies have shown that read-through motion pulse oximeters are superior to conventional pulse oximetry (49). A search for published literature on laboratory pulse oximetry motion studies (excluding abstracts more than 3-yr-old, manufacturer supported or produced studies, reviews and case studies) yields 12 abstracts (47–58) and five papers (59–63) that specifically compare next generation technologies for motion performance. Twelve of the studies, which come from two research laboratories, use similar protocols and show similar results with one manufacturer's technology consistently outperforming other technologies on variables such as failure rate (3 studies), missed events (5 studies), false alarms (4 studies), sensitivity (3 studies), and specificity (3 studies). The results of the remaining five studies, which used unique protocols, were generally mixed with no single technology performing the best on all variables. It should be noted that not all manufacturers were equally represented in the studies. Seventeen of the studies compared some version of Masimo SET, eight studies compared some version of a Nellcor, eight compared Datex Ohmeda devices, and six compared Philips devices.

Although clinical studies have variables that may be harder to control compared with laboratory studies, they have the advantage of using real patients in the hospital setting, and therefore may provide a "truer" test of device performance. Of the various clinical studies published on pulse oximeter performance, those conducted on patients in the NICU and PICU are the most relevant to motion testing for reasons previously discussed. Because of the unique variables in clinical studies, however, it is difficult to combine findings across studies to draw conclusions regarding the relative performances of motion-tolerant pulse oximeter technologies. Additionally, many clinical studies did not provide rigorous enough test conditions to distinguish among technologies. One generalization that can be made however is that, as with the laboratory studies, clinical studies designed to compare the performance of conventional oximetry to read-through motion technologies consistently report fewer false alarms and data dropouts with the new technologies (14,15,17,35,36,59,64,65).

Overnight polysomography is the most accurate and comprehensive method for recording respiration during sleep and is the "gold standard" for diagnosing OSA in children and adults. In a study designed to determine how often pulse oximetry readings were corrupted by motion artifact during sleep, Fletcher et al. (26) calculated the percentage of time that motion artifact was present in recordings of sleep in term and preterm infants. The study found that motion artifact affects more than 50% of recorded traces. Although the NICU may have a sicker population, the sleep laboratory has more instrumentation to establish respiratory movement and airflow patterns, which directly affect oxygenation. Thus, the pediatric sleep laboratory would seem to be a perfect laboratory for pulse oximetry testing. Trang et al. (66) compared a conventional pulse oximeter to a read-through motion pulse oximeter to evaluate which was better at detecting sleep desaturations. The study, conducted on 34 children admitted to a sleep clinic for possible sleep disordered breathing, found that the read-through motion pulse oximeter detected far more true desaturations and had far fewer false desaturations than the conventional technology. In a 2002 study, Brouillette et al. (14) compared the performance of read-through motion pulse oximeters with standard conventional pulse oximetry technology during pediatric OSA studies. They found that although both read-through motion devices had far fewer false alarms than the conventional pulse oximeter, one read-through motion technology was superior in tracking actual desaturations than the other. Studies conducted on adult sleep laboratory patients have shown similar results to these infant sleep studies (67). Thus, regardless of patient population, the clinical sleep studies consistently show that the newer read-through motion technologies reduce false alarms and that some also reliably track true desaturations, especially during OSA testing.

Does Improved Technology Make a Difference?

In a landmark study, Durbin and Rostow showed that caregivers learned to use read-through motion technology to improve the care of postoperative open-heart surgery patients. Compared with conventional pulse oximetry, clinicians were able to significantly reduce the number of arterial blood gas analyses and time to wean from 100% to 40% O_2 when using read-through motion technology (15). Chow et al. (68) credit read-through motion technology as being instrumental in their protocol to reduce blindness and vision problems from retinopathy of prematurity in preterm neonates. Brouillette et al. (14) found that a read-through motion pulse oximeter was able to reduce workload and improve reliability of desaturation detection compared with conventional pulse oximetry. Two separate studies used different motion-tolerant technologies to accurately screen for congenital heart disease in infants (69,70). One of these studies shows that while a read-through motion pulse oximeter had high sensitivity and specificity, thus making it a very useful tool for this type of needed screening, the false desaturations caused by motion artifact made the conventional technology unusable (69). Routine use of pulse oximetry has proven to be highly valuable and carries very little risk to the patient, except when data dropout and false alarms reduce the quality of care. Motion-tolerant technologies have reduced the dropout and false-alarm rates, thus improving patient care without the risks associated with conventional oximetry.

Summary

A wide variety of studies have been published on both the usefulness and potential problems with pulse oximetry in the clinical environment. Most clinicians would agree that motion artifact and the resulting false alarms have been the most significant drawback to using pulse oximetry in the critical care setting. Motion artifact results in a low signal-to-noise ratio, with Spo_2 being driven to lower than actual readings due to venous motion. This venous component is exacerbated by low perfusion. Alarm management in the past tried to deal with these issues by longer averaging, holding data, or alarm delays. Read-through motion and motion-tolerant technologies have dealt with the root cause of motion artifact, thus achieving more reliable readings. To be a useful clinical tool, pulse oximeters should give real-time, continuous, and accurate measurements over a wide range of saturation values, during all types of patient motion, continuous and intermittent, aperiodic and rhythmic, and during low perfusion. There appear to be significant differences in the abilities of the currently available motion-tolerant technologies to achieve these goals, but all motion-tolerant technologies appear to perform better than conventional technologies.

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Maximizing the Laboratory Setting for Testing Devices and Understanding Statistical Output in Pulse Oximetry

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Maximizing the laboratory setting for testing baseline pulse oximetry accuracy in an arterial desaturation study requires a study design that considers management of several aspects in the physiology of the test subject, special attention to the device under test, and great care in the preanalytical (sample handling) and analytical (Co-oximeter) phases. Statistics used to describe the resulting SpO_2 performance include Precision (size of the data cloud), Bias (offset of the data cloud), and A_{rms} (accuracy root mean square), which combines the size and offset of the data cloud in one number. The A_{rms} is the primary statistic required by regulatory organizations to describe general performance over the entire saturation range. It does not describe any one point, but is a compilation of all points over the range tested. Most pulse oximeters in use today specify an A_{rms} of 2%. To meet this specification, two-thirds of the readings will be within 2% of the Co-oximeter reference; however, some individual readings can be as inaccurate as 6% or more. The A_{rms} statistic does not have the capacity to represent all pulse oximeter behavior. Saturation pop-ups, drop-downs, frozen readings, and periods of no reading are not portrayed by the A_{rms}. The next steps in the advancement of regulatory validation testing would be to develop standards that include an expanded analysis of pulse oximeter performance by assessment of pop-ups, dropouts, frozen readings, and periods of no reading through assessment of sensitivity/specificity and possibly a "Performance Index" similar to the approach taken by Barker.

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Testing medical monitoring devices in a human performance laboratory is usually conducted when there is no other, less complicated, reference that can be used to "stand in" for the patient.

Using pulse oximetry as the example, we will give a brief description of comprehensive developmental testing in a laboratory setting, then limit the scope of the discussion to one facet of testing, that of baseline Spo_2 accuracy determination in best-case conditions. We will go into some detail regarding design of study for this type of testing, including methods that are currently used to control variables introduced by the reference device, device under test, and the physiology of the human test subject. Finally, using examples from a physiological monitoring reference laboratory[1], we will describe the statistical output of laboratory testing currently required by regulatory organizations along with practical implications to clinical performance.

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[1]Clinimark Laboratories; before testing all studies received IRB approval from the Avista Adventist Hospital IRB Committee—subjects were consented healthy volunteers.

WHY TEST IN HUMANS?

The less direct the measurement and the more interfering variables involved, the more likely empirical human testing will be required. Development and validation of some devices does not require empirical laboratory testing in humans. For instance, some devices use traceable reference gases that stand in for the human patient and provide a comparison standard that also allows calibration by the clinician after the device has left the factory (1).

There is no standard reference material for pulse oximeters, and they are not suitable for calibration by the user. To paraphrase the current International Organization for Standardization (ISO) Pulse Oximetry Standard "There is today no accepted method of verifying the correct calibration of a pulse oximeter probe/pulse oximeter monitor combination other than testing on human beings. This is due to the complexity of the optical intricacies of the interaction of light and human tissue upon which pulse oximetry depends" (2); While some aspects of functionality can be appraised with the use of simulators (2), pulse oximetry involves a host of physio-optical interactions and, as such, is in the category of devices that require empirical human accuracy tests to develop, calibrate,

Table 1. Human Laboratory Tests Commonly Used During Pulse Oximetry Development—Clinimark Laboratories

Performance category	Examples of clinical conditions	Appropriate laboratory tests
Nominal conditions	• Healthy adult • No ESU, EMI, Dyes, nail polish, movement or light interference • Normal perfusion • Moderate DC variations (intrathoracic pressure changes) • Stable Spo_2 plateau	• Room air precision assessment • Basic accuracy assessment Desaturation (induced hypoxia) Nonarterial [development] Arterial [validation] • Cal curve quick check desat
Rapid saturation changes	• Oxygen decompensation • Apnea (central and obstructive)	• Rapid sat change comparative analysis • Motion
Low perfusion	• Ambient cooling (e.g., operating room) • Moderate rigors (Chill) • Low peripheral circulation • Congestive heart failure • Shock (sepsis, etc.) • Thermoregulatory disorder	• Room air precision assessment • Basic accuracy assessment Desaturation (induced hypoxia) Nonarterial [development] Arterial [validation] Pulse rate (simulators may be used)
Motion	• Highly active peds • Agitation, thrashing (sleep disorders, encephalopathies) • Anxiety and/or pain • Disoriented or restrained • Pharmacologic intervention • Movement disorders (e.g. Parkinson's)	• Room air precision assessment • Basic accuracy assessment Desaturation (induced hypoxia) Nonarterial [development] Arterial [validation] Pulse rate (simulators may be used)
Dynamic range low- and high-attenuation	• Very thin and thick sensor site • Very light and dark pigmentation • Low saturation	• Operational range in the intended population
Sensor temperature	• Low perfusion • Poor skin integrity	• Maximum operational temperature (some manufacturers conduct this test without human subjects)
Ambient light interference	• Bright daylight • Operating room lights • Phototherapy	• Ambient light rejection

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and validate (3,4). Table 1 provides a brief outline of a comprehensive set of pulse oximetry tests, most of which involve empirical testing in human subjects.

A complete description of the pulse oximetry development process is outside the scope of this paper. Instead, we will confine our discussion to that of Basic Accuracy Testing, which is the one test that is required to validate basic SpO_2 accuracy by regulatory agencies (2). The Basic Accuracy Test consists of a Human Arterial Desaturation Study (induced hypoxia), which provides a "best case" estimate of the "trueness" of the pulse oximeter reading in nominal conditions. *Nominal* conditions are defined here as best-case circumstances with no interfering conditions (5). The ISO 9919 standard refers to these circumstances as, "... clinical laboratory conditions under which ... many of the known sources of error in pulse oximetry are virtually eliminated. Examples of such sources of error are low perfusion, EMI, motion, nail polish, pulse oximeter probe mispositioning and ambient light."

MAXIMIZING THE LABORATORY SETTING FOR TESTING

Maximization of the laboratory setting requires a study design with methodology that allows control of variables that can introduce additional error to the determination of saturation trueness in nominal conditions. While a comprehensive analysis of the effects of different study designs is outside the scope of this paper, we will inventory several factors mentioned in the literature that have been shown to increase error in the determination of pulse oximeter accuracy. Taken together, the methods listed here can control many of the known issues that can obscure the final results.

We have categorized these study design factors into four distinct areas. They are Human Physiology Management, Device Under Test Issues, Preanalytical—handling the blood sample, and Analytical— management of the Co-oximeter.

Human Physiology Management

The human body continuously attempts to maintain homeostasis with an arterial saturation in the range of 90%–100% (6). This is in opposition to the goal of a pulse oximeter validation study, which is to cause the oxygen saturation to be less than that which the body considers suitable. During a desaturation study, not only are low saturation levels required but stable plateaus must also be induced. In effect, the body is constantly at odds with the goals of a desaturation study.

Some of the more important physiological test conditions that can be manipulated to limit these potential sources of error include:

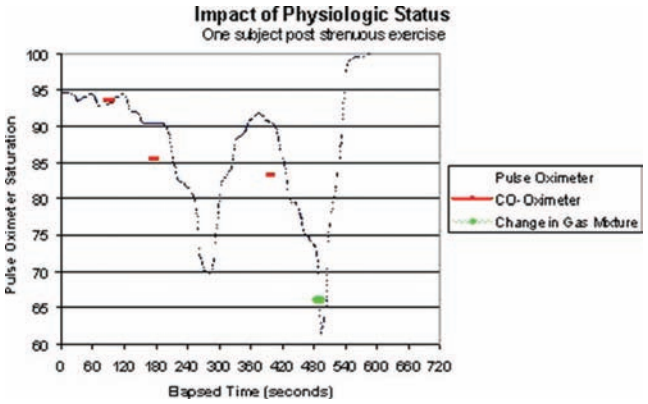

Figure 1. Unstable saturation after strenuous exercise.

- Delay time in the systemic arterial blood supply
- Creation of saturation plateaus
- Reduction of interfering substances
- Physiological conditions that increase the noise to signal ratio

Delay Time

In the presence of a changing saturation, since the pulse oximetry sensor is at a slightly different location than the arterial sample site, there is a difference between when a change in saturation reaches the co-oximeter sample site and when that same change in saturation reaches the pulse oximeter sensor site (7).

To minimize the effects of delay time, choice of an arterial sample site that is close to the pulse oximeter senor site is preferable. Another factor is the patency of the arterial catheter. A well-flowing arterial catheter is required (8,9). If the blood flows too slowly, the chances of missing the "stable" saturation period are increased.

Saturation Plateau

A saturation plateau condition must be created that lasts long enough to allow the co-oximeter sample site and the pulse oximeter sensor site to experience the same oxygen saturation for a period of time that will consider the averaging time of the pulse oximeter (10), the length of time to draw the arterial sample, and time for the pulse oximeter to restabilize after the potential interruption of blood flow during sampling (2,7,11).

Factors that can affect a stable saturation plateau are:

- Changes in the physical status of the test subject
- Fio_2 administration equipment
- Methods to identify the quality of the plateau

Some changes in the physical status of the test subject, while not considered unhealthy, can impact the subject's physiology to a degree that the ability to maintain a stable saturation plateau is impaired. An example of this is shown in Figure 1. After strenuous exercise, while breathing an Fio_2 of 0.1 for 12 min, the test subject exhibited highly unstable saturation levels that were not stable enough to use in comparison of pulse oximetry to co-oximetry.

Table 2. Compensations for Physiological Limitations

Delay time	Choose an arterial sample site close to the pulse oximeter sensor site
	Maintain a free flowing arterial catheter
	Warm test site
Saturation plateaus	Avoid borderline health conditions in the test subject
	Fio_2 administration equipment designed to balance variations in the saturation of the test subject
	Real-time monitoring equipment that will identify the quality of the saturation plateau
Interfering substances	COHb and MetHb should be at or below normal levels
	Nail polish and artificial nails should be removed
Interfering physiological conditions	Low perfusion—warm the test subject
	Motion—no motion during data collection

Because of the body's continual attempt to maintain a saturation in the 90% range, the system that is used to administer low Fio_2 levels must be configured, so that attempts of the subject's physiology to maintain homeostasis above 90% SaO_2 can be overcome. Two primary methods have been described. One is a system that gradually delivers varying Fio_2's in such a way that the saturation is slowly manipulated (12). The other involves voluntary hyperventilation of the test subject with larger, rapid, less gradual steps in the saturation (13). To achieve a stable saturation plateau, a method of determining when the plateau has been reached is also necessary (2,3,13).

Interfering Substances

Common interfering substances are carboxyhemoglobin, methemoglobin, nail polish, and artificial nails (14–16). When testing the pulse oximeters ability to read correctly in baseline conditions, the carboxyhemoglobin and methemoglobin should be restricted to normal values, unless the device is able to distinguish carbon monoxide and methemoglobin from oxygen. Nail polish and artificial nails should be removed before testing.

Interfering Physiological Conditions

Low perfusion and motion are two interfering physiological conditions that occur frequently and must be eliminated in baseline performance testing (2,12,17–21). The hands, and sometimes the entire body, of the test subject may be actively warmed to eliminate low perfusion and to improve circulation (22–24) (Table 2).

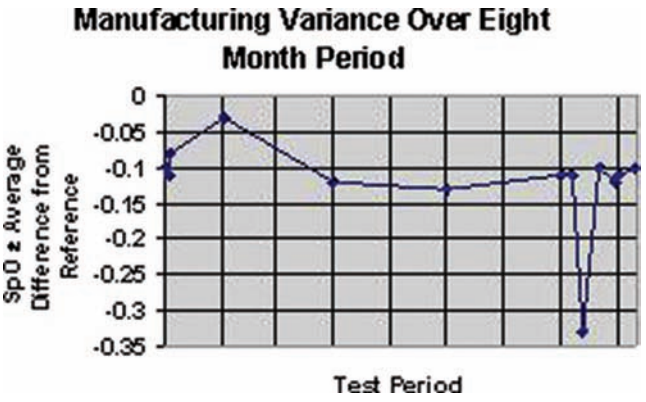

Figure 2. Spo_2 Precision in human room air tests.

Device Under Test Issues

Intradevice variations in both the pulse oximeter and the sensor and device-related issues that directly influence quality of the readings can be controlled so that the influence is significantly minimized.

Intradevice Variation

Intradevice variation can originate in the manufacturing process when small differences in component tolerance add up to a measurable difference in final device performance. An example of this is shown in Figure 2, which shows manufacturing variance over an 8-month period. The average difference in most of the pulse oximeters manufactured during this period varied by 0.1% saturation in human room air Precision testing. However, one manufacturing run resulted in a jump of 0.33% saturation in the average difference testing. This would have resulted in a much larger difference in the low saturation ranges of a hypoxia test. The use of multiple units in a test can diminish the influence of intradevice variability. Multiple sensors of each sensor style should also be tested simultaneously, due to similar potential intrasensor variability.

Influences in Quality of Readings

Four device-related factors that can influence quality of the reading are the method of data collection, sensor placement, optical cross-talk, and electrical interference (noise sources from other equipment in the laboratory or under test).

Hand data collection requires that the data be entered manually into the statistical analysis program. This can be a source of inaccuracy in the study that can readily be eliminated by the use of electronic data collection. Great attention to sensor placement at the start of each test is important to ensure that all systems read as close to each other as possible. Inaccuracy as much as 12% has been reported as a result of sensor malposition (25). Optical interference is light reaching the sensor detector from any source other than from the LED's of the sensor. This can be environmental or from LED's of adjacent pulse oximeter sensors, which is known as "cross-talk." Pulse oximeter probes should be covered with opaque material to prevent light interference (3,26–28). Finally, devices and sensors must be electrically shielded to prevent introduction of added noise from nearby electrical devices (3) (Table 3).

Table 3. Device Under Test Recommendations

Intradevice variation	Conduct simultaneous testing of multiple units/sensors
Influences in quality of readings	Use electronic data collection Careful sensor placement at the start of each test Cover sensors with opaque material to prevent cross-talk Electrical shielding

The Preanalytical Phase

The preanalytical phase is the entire process involved in handling the sample. This includes everything from obtaining the sample through insertion of the sample into the co-oximeter. The preanalytical phase can be the largest contributor of error to the arterial sample measurement (29).

Care should be taken during this entire phase. Specific steps that should be attended to are:

- Syringe type and storage
- Heparin
- Identification of each syringe
- Sample collection
- Sample preparation after collection

Syringe Type and Storage

Studies indicate that plastic may be permeable to oxygen and carbon dioxide, which could introduce errors in the sample (30–34). Current standards call for the use of glass syringes when sample measurement will be delayed longer than 30 min after collection. In this case, it is also advised that the glass syringe be placed on ice (presumably to slow metabolic processes). Samples drawn in plastic syringes should be analyzed within 30 min and should not be iced (29,35).

Heparin

The syringes should be preheparinized with dry heparin or, since liquid heparin can dilute the sample and alter the true value of a sample, care should be taken to expel all excess heparin from the syringe (36–39).

Sample Identification

Because of the large number of samples obtained in the relatively short period of a study, each syringe should be labeled in a manner that will allow clear identification. This can affect both sample management during analysis (error resulting in remeasurement) and statistical processing (facilitation of accurate data synchronization).

Table 4. Reduction of Preanalytical Errors

Syringe choice	Plastic may be used if analyzed within 30 min after collection Glass if to be stored and analyzed longer than 30 min after collection—place on ice
Heparin	Dry lithium to reduce risk of dilution
Identification	Serialize each syringe
Sample collection	Waste a sufficient volume of blood prior to collection
Preparation after collection	Air bubbles must be expelled, mix thoroughly, remove the first drops of blood before analysis

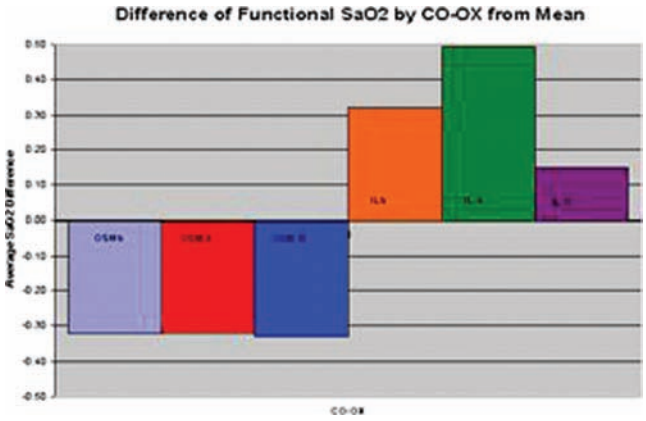

Figure 3. Intra- and inter-co-oximeter variability. Tests conducted using manufacturer recommended calibration and quality control procedures.

Sample Collection

Care should be taken to waste a sufficient volume of blood before collection of the sample in order to prevent contamination by flush solution (if used) or by old blood that may remain in the catheter from the previous sample. This is especially important when extension tubing is used.

Preparation After Collection

Immediately after sample collection, air bubbles must be expelled from the syringe (40–42). The sample should then be mixed thoroughly to dissolve the heparin. Failure to do so may lead to the formation of microclots which, in turn, can bias results, interfere with measurements, and lead to analyzer downtime (43) (Table 4).

Analytical—Management of the Co-oximeter

The accuracy specification for commonly used co-oximeters is 1% (44,45). When one considers that the published accuracy specification of most pulse oximeter systems is 2%, it is apparent that measures to control additional inaccuracy introduced by the co-oximeter are of great importance.

There are three areas that can help limit uncertainty introduced by the co-oximeter. They are:

- Quality assurance procedures
- Manufacturer recommended procedures (maintenance, calibration, quality control)
- Increased vigilance procedures (increased cleaning, use of multiple co-oximeters, and multiple syringe runs)

Quality Assurance Procedures

The Clinical Laboratory Information Act states that research laboratories are not required to meet the Clinical Laboratory Information Act requirements; however, quality assurance procedures that are required in laboratories reporting clinical data are recommended by regulatory standards (2,46). These quality assurance procedures include participation in a peer group survey similar to the CAP program, written protocols and procedures, and tracking documentation of quality control and calibration (29) (Peer Group Surveys, College of American Pathologists, 325 Waukegan Road, Northfield, Illinois 60093).

Manufacturer Recommended Procedures

Procedures recommended by the co-oximeter manufacturer are required by regulatory standards (2). These include routine maintenance, calibration, and quality control. It is crucial that the co-oximeter be cared for and operated in accordance with manufacturer directions.

Increased Vigilance Procedures

Increased Cleaning. Pulse oximetry validation studies of this type usually involve approximately 25 syringes per test with each syringe being run 1–3 times within a period of an hour. This means that a co-oximeter receives approximately 100–375 samples in an 8 hour period with 250–1125 samples in a 4-day period. This is a higher sample load than normal clinical use; thus, attention to cleaning and protein removal is of much greater importance than in normal use. We have found that increasing the cleaning and protein removal frequency decreases error messages and other problems with the co-oximeter during this type of study (47).

Use of Multiple Co-oximeters. Errors in the co-oximeter from manufacturer to manufacturer has been reported to be as much as 1.5% (48). A Clinimark study of three of the same models from two different manufacturers showed the intradevice variation of one manufacturer to be more than 0.3% and interdevice variation to be 0.5% between manufacturers (Fig. 3).

Another Clinimark study evaluated the agreement of three co-oximeters. Arterial blood samples were obtained from eight healthy volunteers over the range of 70%–100% saturation with approximately 25 samples per subject. In this study, two co-oximeters were compared with a third. Manufacturer-recommended calibration, quality control, and maintenance procedures were followed, and all co-oximeters met the calibration and quality control acceptance criteria. Figure 4 illustrates the

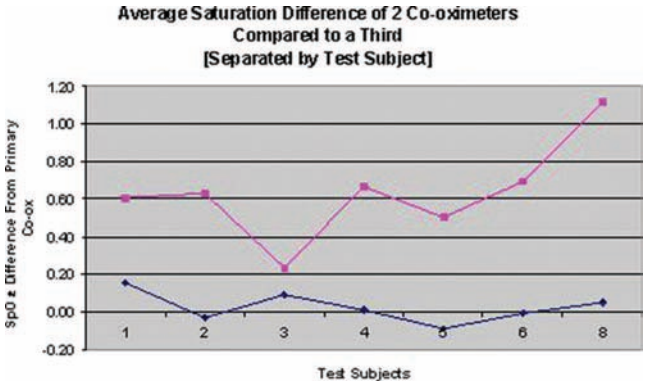

Figure 4. Agreement of three co-oximeters.

Table 5. Sample Error in One Syringe

Run no.	SAT	RHb	O_2 cap
1	92.8	7	22.3
2	96	3.9	22.2
3	93.3	6.6	22
4	93.2	6.7	22

Table 6. Techniques to Reduce Analytical Errors

Quality assurance procedures	Participation in a peer group survey Written protocols and procedures Tracking documentation of QC and calibration
Manufacturer recommended procedures	Required: maintenance, calibration, and quality controls
Increased vigilance procedures	Increased cleaning: lipid and protein removal, etc. may be required more frequently Use of multiple Co-oximeters: to diminish intradevice variation errors Multiple syringe runs: to decrease unidentified errors

point that the simultaneous use of multiple co-oximeters can provide important information regarding the measure of truth during a study.

If only one co-oximeter were used in a study, there would be no clear indication of outlier readings or reading drift. The use of more than one system provides better identification of drift, sample errors and outlying readings. It is recommended that multiple co-oximeters be used simultaneously during a validation study.

This highlights an important issue that there is currently no standard reference material for oxygen saturation. Thus, other than the highly technique-dependant, complex, and time-consuming Van Slyke method (49), there is no practical method to verify absolute accuracy of the SO_2 reading.

Multiple Syringe Runs. Real-time quality assessment can be accomplished by measuring each syringe in each co-oximeter multiple times. For example, small fairly undetectable air bubbles and analytical errors can be identified. An excerpt of data from one study is shown in Table 5. The table includes data from one co-oximeter after one arterial syringe sample was measured four times. Run number 2 gave a saturation value approximately 3% higher than the other three runs, and was clearly inaccurate. Without this multiple view of the readings, many errors can go unnoticed (Table 6).

UNDERSTANDING STATISTICAL OUTPUT OF LABORATORY TESTING

Uncertainty

The goal of statistical representation of data is to provide clinicians with a fairly concise number that gives a picture of the overall expected performance. When we test a device, the information collected is a group of data points that usually miss the mark to some degree. In effect, when *accuracy* is tested we are making a determination of how many data points miss the mark and by how much: in other words, the *inaccuracy* of the data. Thus, "accuracy" statistics, in reality, portray inaccuracy which is defined more correctly as the uncertainty of a device (50). During this discussion of statistical output, it will help the reader to keep the concept of uncertainty in mind.

The performance specification of a pulse oximeter refers to a collection of data points comparing the device to a reference that provides true values. The features of this collection of comparative data points (or data cloud) are described using various statistical formulas that condense the information into a single number. The statistics that we are concerned with in pulse oximetry are Precision, Bias, and A_{rms} (accuracy root mean square). We will explain Precision and Bias, then show how these two statistics are combined in the A_{rms} calculation.

Precision—Size of the Data Cloud

The size of the entire grouping of data points of the test device, or data cloud, represents random errors in the readings of repeated measurements taken under the same conditions. Random error is caused by various sources of noise that result in a scatter of the readings, and is referred to as Precision. In effect, this statistic is the standard deviation (SD) of the data cloud grouped around the best-fit line of the data cloud (indicated by line B in Fig. 5). Precision does not tell how far from truth (indicated by line A in Fig. 5) the data cloud is, just how big it is. The Precision of two devices are shown in Figures 5 and 6. Repeated readings from the device in Figure 5 with a Precision (S_{res})of 2.1 indicate less random noise, or random error, than readings from the device in Figure 6 with an S_{res} of 5.2, indicating poorer Precision.

The formula for Precision as used here is seen in Figure 7. In this calculation, Precision is represented by $S_{res,}$ which is the SD of the residuals. A residual is

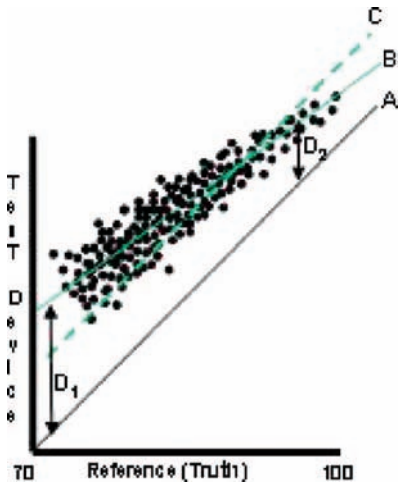

Figure 5. Synthesized data for illustrative purposes. A, truth; B, test data best fit line; C, Mean Bias; D, one Local Bias point.

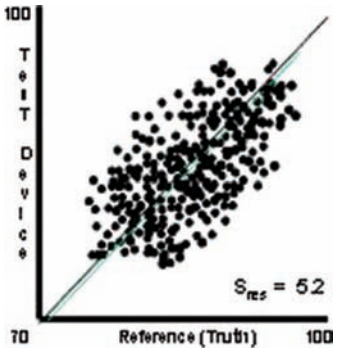

Figure 6. Synthesized data for illustrative purposes.

$$S_{res} = \sqrt{\frac{\sum_{i=1}^{N} (SpO_{2i} - SpO_{2fit,i})^2}{(n-2)}}$$

Figure 7. Precision.

$$B = \frac{\sum_{i=1}^{n} (SpO_{2i} - S_{Ri})}{n}$$

Figure 8. Mean Bias.

the difference of one test data point from the best-fit line drawn through all of the test data.

Bias—Offset of the Data Cloud

Bias is the offset of the test data from truth caused by systematic error. Mean Bias and Local Bias are two important characteristics of bias. Mean Bias is one number that represents the mean distance, or average offset, of the entire data cloud from truth (represented by C in Fig. 5). The formula for Mean Bias is shown in Figure 8. Mean Bias is the same over the entire Spo_2 range; in other words, it is the same at 70% as it is at 100%.

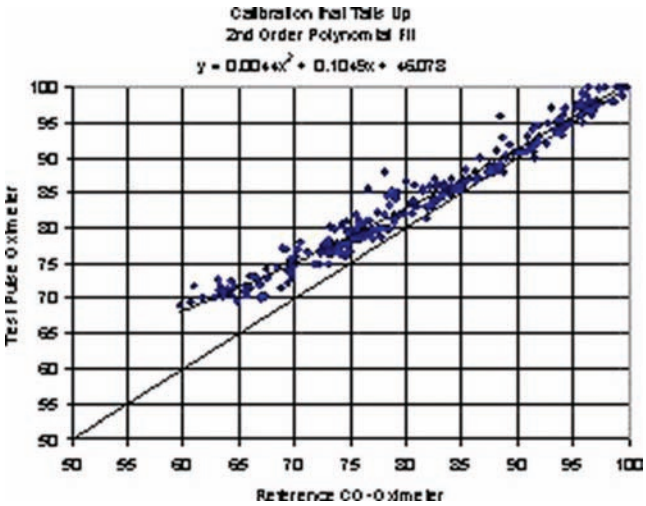

Figure 9. Variable offset.

$$b_i = SpO_{2fit,i} - S_{Ri} \qquad i = 1, \ldots, n$$

Figure 10. Local Bias.

The Actual Bias of a pulse oximeter, however, often varies in the different Spo_2 ranges. Local Bias reflects the variability in the different ranges. Local Bias is the offset of each point over the Spo_2 range and can indicate complex pulse oximetry calibration curves that are not well represented by the single Mean Bias number.

Local Bias is essentially the difference of each point on the best-fit line of the data cloud (B in Fig. 5) from truth at that point (two different Local Bias points are represented by D1 and D2 in Fig. 5). In Figure 5, all of the Local Bias values are different, which causes the slope (or calibration curve) of the test data to be different from the slope of the reference data. Local Bias can represent linear or nonlinear calibration curves. Data from a pulse oximetry reference study, shown in Figure 9, illustrate this point. Note that the tail of the data cloud in the lower saturation range curves up from the reference co-oximeter. The Local Bias formula is shown in Figure 10.

A_{rms}—Combined Size and Offset of the Data Cloud

In his 1989 paper, *Errors in 14 pulse oximeters during profound hypoxia*, Severinghaus et al. recognized the need to indicate the magnitude of both Precision and Bias when describing the performance of a pulse oximeter (13). As an index of error, he coined the term "Ambiguity" to describe the absolute sum of Bias and Precision. Although the formulas used in this paper were somewhat different from those currently used in pulse oximetry performance specifications, the purpose remains the same: to include both Precision and Bias in a single number.

The A_{rms} statistic is required by regulatory agencies when overall accuracy of a device is evaluated. The

$$A_{rms} = \sqrt{\frac{\sum_{i=1}^{n} (SpO_{2i} - S_{Ri})^2}{n}}$$

Figure 11. A_{rms}.

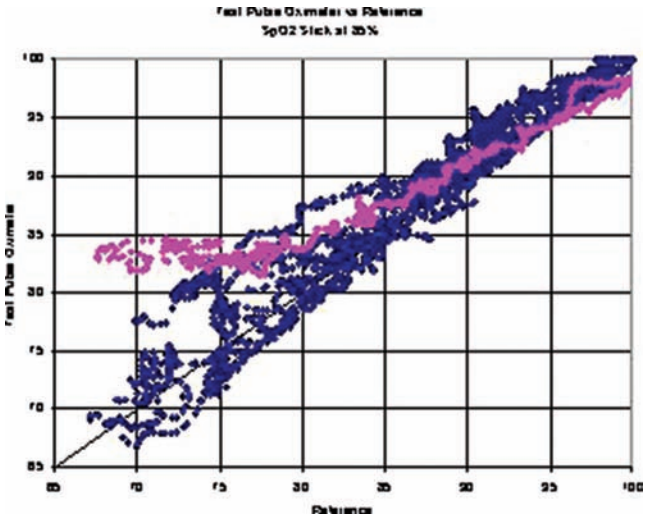

Figure 12. Readings frozen at approximately 83%.

A_{rms} calculation is affected both by Precision and by Bias (including both Mean and Local Bias). The name comes from the fact that it is the square root of the mean of the squares of the values. The values being the differences of each data pair (test reading—reference reading). Another way of describing the A_{rms} calculation is that it looks at a "moving" mean or SD of pairs where the reference value is different for each test–reference pair. The formula can be seen in Figure 11.

Each test–reference data pair is used in the calculation of the overall A_{rms} number and influences the final magnitude of the results. This means that a data cloud with an acceptable A_{rms} can have a large Bias with a tight Precision or a poor Precision with a small Bias, but it cannot have much of both and still have an acceptable A_{rms}. Figures 5 and 6 illustrate this point; the data sets in both figures have the same A_{rms}. Although Figure 5 has a larger Bias than Figure 6, it has a Precision that is much tighter. In this case, it has large Bias but tight Precision. Conversely, Figure 6 has a small Bias but poor Precision (more scatter).

Thus, the A_{rms} statistic provides one number with a similar property to Severinghaus et al.'s *Ambiguity*, which includes both Precision and Bias in a single number and can tell the clinician generally how *Accurate* the pulse oximeter is or, to use the recommendation of National Institute of Standards and Technology, the *Uncertainty* of the pulse oximetry reading.

Data sets from human studies often have more complex features than simply poor Precision or large Bias. One example can be seen in Figure 12, where

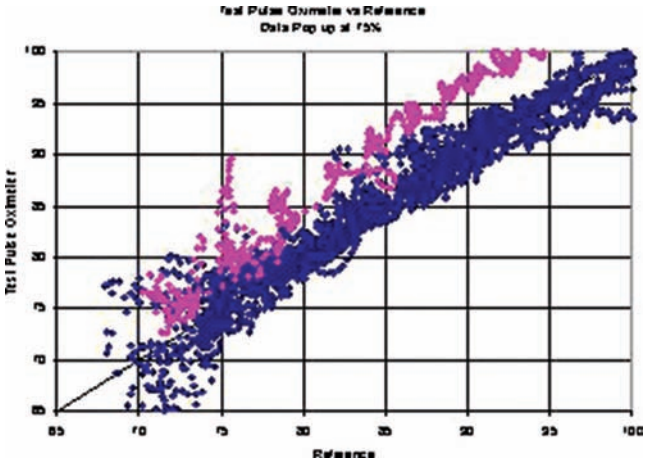

Figure 13. Pop-up.

data from one of the test subjects followed the Reference fairly well from 100% to 85%, at which time the test pulse oximeter stopped reporting the true saturation and stayed at a reading of about 83%. With that subject in the data pool, the A_{rms} was unacceptable. Another example is shown in Figure 13. The saturation of the test pulse oximeter popped-up within a 1-min period from 75% to 90% then dropped back to read correctly. In this case, with the additional presence of other pop-ups of less magnitude, the A_{rms} was again outside the acceptable range.

In the cases of Figures 12 and 13, the Local Bias of the anomalous readings influenced the calculation to a degree great enough resulting in an unacceptably large A_{rms}.

Practical Implications of A_{rms}

Most pulse oximeters in use today specify an A_{rms} of 2%. What does this mean to the clinician? How inaccurate can a pulse oximeter be and still meet this specification? What does this number not tell the clinician?

The A_{rms} is used to describe general performance over the entire saturation range and does not describe any one point but is a compilation of all points over the full range tested. Usually, saturation readings in the 90%–100% range show a smaller A_{rms} than 2%; readings in the 70%–80% range are more than 2%; while readings in the 80%–90% range are about 2%.

How inaccurate can a pulse oximeter be and still meet a specification of 2%? To answer in clinical terms, Figure 14 is a set of data from an arterial desaturation study that included 12 test subjects. The A_{rms} of this test set was 1.5%. Figure 15 is the same data set with the data from one subject given a 3.5% offset (data in oval). The addition of the offset in this one subject increased the A_{rms} to 2.0%. Because of normal variations in the population, this type of offset is a common occurrence. Even though the A_{rms} is 2.0%, some of the data in the oval are inaccurately high by as much as 3% in the 90's, and as much as 6% in the 70's. Thus, even in nominal patient conditions, a pulse oximeter

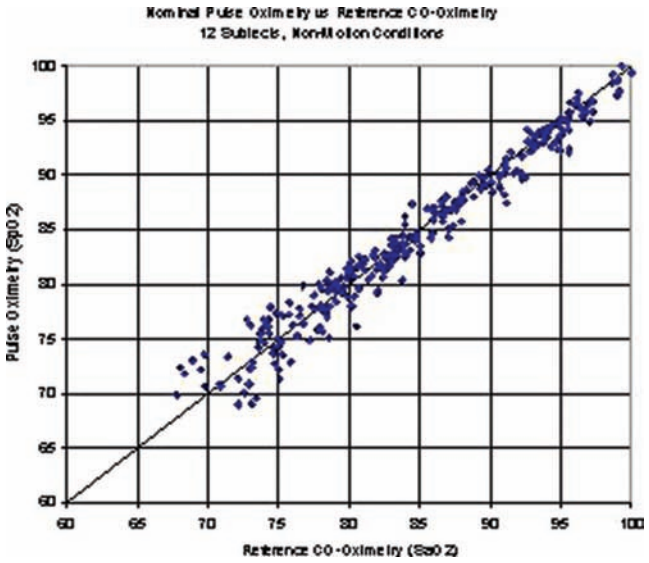

Figure 14. A_{rms} of 1.5.

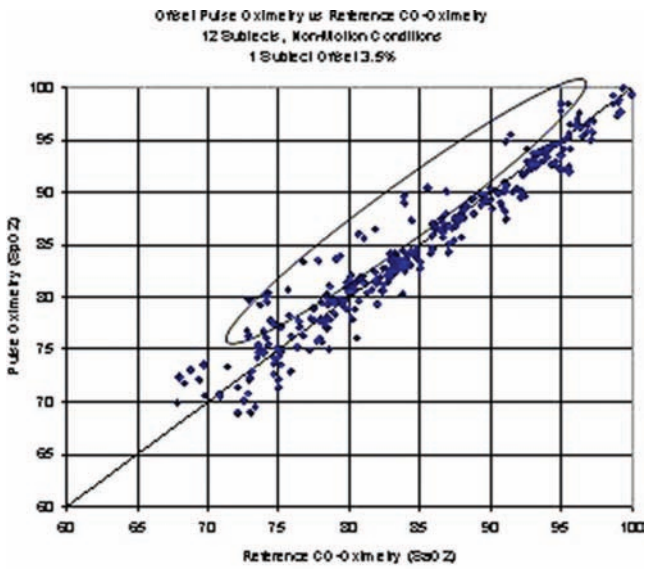

Figure 15. A_{rms} of 2.0 one subject with an average bias of 3.5%.

can provide out of specifications readings in one patient and still be in specifications from a statistical point of view.

At times, saturation pop-ups, drop-downs, frozen readings, and periods of no reading are seen in an ill-behaved pulse oximeter system. The A_{rms} statistic is not designed to represent these dynamic or changing conditions; instead it is calculated from test–reference data pairs that are each collected at one point in time. The undesirable performance condition may not be reflected in the statistics unless the condition happens to occur at the moment the data are being collected. Additionally, nonreading conditions are not represented in the A_{rms} statistic.

In summary, even with a well-behaved system, some readings were seen to be off by as much as 3%–6%, as shown in the example above; additionally, the A_{rms} statistic does not reflect many dynamic performance conditions, such as no readings, that can be important in the clinical application of a pulse oximeter.

CONCLUSION

We have described components of study design that will maximize the laboratory setting for accuracy testing in nominal pulse oximetry conditions; outlined improvements that can be made to current pulse oximetry laboratory methods; and explained the statistics used in pulse oximetry.

As we continue to improve our ability to assess baseline performance, it is wise to keep in mind that while we have discussed the foundation of pulse oximetry development, possibly the most important aspects of pulse oximetry readings are those times that happen less often but in the most critical patients. In those conditions uncertainty of the saturation reading can be much greater than that seen in nominal conditions.

This paper describes one portion of pulse oximeter development, that of accuracy assessment in nominal conditions, which are required by regulatory organizations before clearance for use in the clinical arena. The information from this type of testing provides information about a "collection of specific intervals" during the test that compares the pulse oximeter to a co-oximeter, which can only measure point-in-time data.

Next steps would be for regulatory organizations to expand the scope of required testing that includes a more comprehensive assessment of pulse oximetry performance such as the ability of a pulse oximeter to provide saturation readings continuously. Thus, one might envision assessment of pop ups, dropouts, frozen readings, and periods of no reading through assessment of sensitivity/specificity and possibly a "Performance Index" similar to the approach taken by Barker (18,51–53). Finally, development of an accessible method to verify the absolute accuracy of the co-oximeter such as a reference material for oxygen saturation is also needed.

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Effective Standards and Regulatory Tools for Respiratory Gas Monitors and Pulse Oximeters: The Role of the Engineer and Clinician

Sandy Weininger, PhD

Developing safe and effective medical devices involves understanding the hazardous situations that can arise in clinical practice and implementing appropriate risk control measures. The hazardous situations may have their roots in the design or in the use of the device. Risk control measures may be engineering or clinically based. A multidisciplinary team of engineers and clinicians is needed to fully identify and assess the risks and implement and evaluate the effectiveness of the control measures. In this paper, I use three issues, calibration/accuracy, response time, and protective measures/alarms, to highlight the contributions of these groups. This important information is captured in standards and regulatory tools to control risk for respiratory gas monitors and pulse oximeters. This paper begins with a discussion of the framework of safety, explaining how voluntary standards and regulatory tools work. The discussion is followed by an examination of how engineering and clinical knowledge are used to support the assurance of safety.
(Anesth Analg 2007;105:S95–9)

Effective risk control measures in medical devices should be implemented with an understanding of the underlying hazardous situations gained by an evaluation of the root causes. These situations can best be identified and analyzed by a multidisciplinary team of experts consisting of engineers and clinicians. Engineers are needed to focus on the device implementation from a mechanical, electrical, or software perspective, identifying how the device can fail and what are its performance limitations. Clinicians focus on the impact of using the device on the patient and addressing the adequacy of the use instructions, predict unanticipated situations, and describe the boundaries of appropriate use (foreseeable misuse). When medical device safety standards are written (1,2), the standards development organization must ensure a balanced and diversified working group in order that all these viewpoints are represented. Further, they incorporate past efforts to identify and control risks, so that their efforts are comprehensive and control measures are as effective as possible. Regulators also use a multidisciplinary team to understand a manufacturer's design and assess the risk implications of their design decisions. It should be obvious that manufacturers should have a complimentary multidisciplinary design team in place to assure safety is addressed early and often in the development lifecycle.

This paper demonstrates how the root causes of hazardous situations might be found in the engineering or clinical realms, hence the need for multidisciplinary team participation in the risk management activities. Two device types are examined, respiratory gas monitors (RGMs) and pulse oximeters, with safety issues such as calibration and accuracy, response time, and protective measures to demonstrate the need for both engineers and clinicians to identify and solve the problems. Before examining these hazardous situations and how they were identified and controlled, I will present some background on the regulatory and standards processes, the underlying safety standards framework, and how this framework is used in supporting safety.

MEDICAL DEVICES AND REGULATORY PROCESSES FOR ASSURING SAFETY

Many activities are needed throughout a product's lifecycle to bring a medical device to market. Regulatory and standards processes leverage the existing engineering and clinical knowledge bases to achieve reasonably safe and effective products. Two activities are considered necessary for assuring the safety of the basic design: assessing the device's basic safety and essential performance, and having an adequate design process that can identify hazardous situations and

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control the risks associated with those hazards. Regulators, manufacturers, and clinicians recognized the need for a general family of standards (1) to address the overall safety of medical electrical (ME) equipment; thus, the International Electrotechnical Commission (IEC) 60601 family was born to establish a minimum set of safety criteria for use by device developers and regulators.

The traditional model for assuring safety of ME equipment, as embodied in the first and second editions of IEC 60601, was to address basic safety, unintended physical hazards such as electric leakage, mechanical pinching, scalding surfaces, and material toxicity. The hazardous situations addressed by the General Standard second edition did not include clinical performance; ME equipment that did not work or function as clinically intended was to be addressed by standards particular to each device. The definition of hazard in the third Edition of IEC 60601 was expanded to include functional safety, protection against malfunctions such as incorrect outputs, abnormal operation, fault conditions, and inaccurate operating data (3).

Regulators and standards writers worldwide understood that adequate risk mitigation could not be defined *a priori* for every situation, no matter the expertise of the multidisciplinary group working on it. A robust risk management process was identified as an essential element of medical device development. Device-specific standards writers were instructed to address the essential performance necessary to achieve freedom from unacceptable risk. Although basic safety typically has defined acceptance criteria (for e.g., a 41°C safe temperature limit for a sensor intended to contact the patient), essential performance requires a judgment as to what constitutes unacceptable risk. This judgment is made in the context of the risk management process where a multidisciplinary team is needed to comprehensively identify and evaluate risks. As the world makes the transition from the second to the third edition of IEC 60601, those involved in the development of ME equipment should understand that the third edition has provisions for assessing both the adequacy of the design *and the design process*.

The third edition of IEC 60601 sets up a safety framework by requiring manufacturers to systematically assess, using an International Organization for Standardization (ISO) 14971 (4) compliant risk management process, the reasonably foreseeable risks and develop mitigations that control risk to an acceptable level for the expected life of the ME equipment. The risk control framework consists of an integrated approach in which the manufacturer uses one or more of the following *in the priority listed*:

- inherent safety by design
- fault-tolerant measures (5)
- protective measures in the equipment
- information for safety (i.e., labeling, for example, warnings and instructions for use, limits on acceptable values of monitored variables).

REGULATORY PROCESS AND STANDARDS USE

The uses of standards differ by the jurisdictional authority under which the medical device is sold. For example, the Food and Drug Administration (FDA) "recognizes" standards that are suitable for use in premarket submissions, a recognized standard is an accepted method of risk control for a particular hazardous situation. The FDA process evaluates risk based on the intended use, the use environment, indications for use, and the functions and performance of the medical device. The evaluation includes protective devices and alarm systems, functional limits and any operational or special features. The evaluation addresses whether reasonable hazards and risk control measures were identified, and evidence that these were successfully implemented and *effective*. Standards are developed in much the same way and are used extensively in other regulatory systems, such as the European Economic Area.

The process in the European Economic Area relies on a series of Medical Device Directives that contains Essential Requirements, a list of identified hazardous situations, with which equipment is required to comply. Conformance to harmonized standards (standards built to address this list of hazardous situations), in combination with a quality system (as embodied by ISO 13485) (6), for all but the lowest risk medical devices, can be used to demonstrate conformance to the essential requirements. A medical device fully compliant with the relevant harmonized standards is presumed to comply with the essential requirements, and therefore safe for market—as safe and complete as the standards the assessment is built upon.

We are therefore provided with a comprehensive standards framework and a requirement that risk management be performed to assure basic safety and safe clinical operation. How does this translate into actual practice? Devices that monitor respiration and ventilation (oxygen and CO_2) whether in expired/inspired gases or in tissue through electrochemical or optical means, are medical devices classified as ME equipment by the IEC, ISO, and by regulatory authorities. The FDA recognizes several standards for use in assuring the safety and performance of RGMs and pulse oximeters:

- ISO 21647 for RGMs
- IEC 60601-2-23: Particular requirements for the safety of transcutaneous partial pressure monitoring equipment, and IEC 60601-3-1: Essential Performance Requirements for Transcutaneous Oxygen and Carbon Dioxide Partial Pressure Monitoring Equipment for transcutaneous monitors
- ISO 9919: Safety of Pulse Oximeters.

Let's see how these safety critical hazardous situations as embodied in these standards were evaluated using a multidisciplinary approach.

ACCURACY AND CALIBRATION

Accuracy, and its assurance through proper calibration, are primary contributors to the safety of ME equipment and are functions on the explicit configuration of the monitor. How much accuracy is needed is a clinical decision; how to deliver this amount of accuracy is an engineering decision; how to assess the delivered performance requires both engineers and clinicians. For example, the FDA's guidance document on pulse oximeters (www.fda.gov) asks the manufacturer to describe the available accessories (sensors, patient cables, etc.), identify the sensor-monitor combinations, and show the validation evidence for each combination. Where an engineering argument can be made that the same electro-optical configuration, materials, and algorithm are used or that there are data to show that the different sensor-monitor combinations perform equivalently, the manufacturer can use one set of data to represent the group of similar construction. As each configuration may have a different use profile, the perspective of the engineer and clinician are needed to understand the configurations and determine if the validation data are applicable.

Accuracy specifications need to be appropriately reported, so that clinicians can understand the performance of the devices they use and assess the relative performance against others monitors. The accuracy specification for clinical purposes for pulse oximeters should be reported using the single statistic, A_{rms}, or root mean square accuracy (defined in ISO 9919). It is meant to convey the performance of the oximeter system to the clinician over the broad range of operation of the device. A large uncertainty (poor accuracy) can mean lower than indicated saturation, which, for some patients, can be a hazardous situation. Both the ISO/IEC standards and FDA guidance documents establish limits on accuracy and contain additional recommendations on clinical performance. ISO 9919 cites a recommended calibration protocol in an informative annex, which is referenced during FDA marketing clearance. Accuracy verification (saturation) requires data from ideal laboratory testing to demonstrate the performance of the oximeter (sensor and monitor combination) from at least 70% to 100% Spo_2 in human subjects. These protocols are explained in ISO 9919, Appendix EE, and were developed by engineers and clinicians over time to reliably and safely evaluate the performance of oximeters.

An accuracy specification is not always indicative of performance over the entire clinical range or use population. Low saturation accuracy is typically of higher uncertainty than higher saturation values. Having bias and precision over each decade of operation would provide greater detail on the performance of the device and make objective comparison (which is both an engineering and clinical activity) to other monitors more meaningful than a single statistic. In other instances, it is not possible to get evidence of accuracy over the entire clinical range needed. Oximeters are the standard of care for neonatal monitoring, yet it is recognized that desaturation studies to obtain calibration data cannot be ethically performed. To get an indication of performance in this population, both adult performance and observed performance on neonates should be reported. Observed performance can be samples collected for convenience when a needed procedure is medically indicated.

In contrast to pulse oximeters, RGM performance can be evaluated on the bench. Engineering bench testing is sufficient in many cases to assess accuracy in RGMs, where demonstration of functional performance and proper calibration procedures are essential for assuring safe operation and identifying hazardous clinical situations. Bench testing would identify an inaccurate RGM within an anesthesia machine that has an incompetent inspiratory or expiratory valve, permitting a dangerous accumulation of CO_2 within the breathing circuit. The performance of the RGM in the presence of interfering gas and vapors (such as alcohol and water vapor) can be safely considered. The composition of respiratory gases is not just oxygen, nitrogen, and carbon dioxide; many gases and substances could, depending on their concentration and the method of measurement, alter the displayed value. The RGM standard provides a table of known interfering gases and vapors to be tested. Diverting or side-stream RGMs are especially susceptible to interference by water. It is important for the user documentation to clearly indicate which gases and vapors are intended for use. This disclosure is then used to guide the evaluation of the monitor, i.e., with which interfering gases and vapors the monitor needs to be tested.

Accuracy in the field, when the monitor is in actual clinical use, also needs to be maintained. RGMs are almost always provided with a factory calibration. The need for a recalibration depends upon the specifics of the monitor design. RGMs, in particular, capnographs, often recommend a periodic calibration or check that consists of exposing the sensor to room air with an assumed oxygen and carbon dioxide concentration. Care must be taken when performing such a check or calibration, since the failure to remove the sensor from a patient-connected breathing circuit can result in an offset in the gas values reported post-recalibration. Thus, the clinician and engineer must talk to each other to understand what must be done to calibrate and how it can be safely done in the patient environment.

In contrast to the RGM calibration procedure, pulse oximeters rely on the calibration curve developed using previously validated controlled desaturation tests. Oximeters cannot be field calibrated nor can their accuracy be field checked as there is no simulator that has been validated for such a purpose. Yet they can be functionally assessed by placing the probe on a healthy human to make sure all the electronic components work. Accuracy verification for pulse rate in

pulse oximeters can rely on a simulator as long as it spans the operating range; it is essentially a functional verification of the waveform detecting algorithm.

Functional simulators are useful to assess engineering performance, as when the harshness of reprocessing activities on single-use sensors adversely affects sensor performance, bringing into question whether the original electromagnetic compatibility and basic safety (e.g., shock, vibration, fire, fluid ingress) evidence is still valid. Other functional aspects of reprocessed devices are best evaluated with a simulator to allow reproducible test conditions to be established and maintained.

RESPONSE TIME

The shrinking of electronic circuitry is enabling greater integration and increased use of wireless communications, leading to an increased need to understand electromagnetic compatibility issues [see IEC 60601-1-2 (7)]. Interference can cause lockup, resulting in conditions where unwanted energy is delivered to the patient or unknown errors occur in the measurement value. In monitors with patient-connected sensors, the ME equipment must be assessed for compatibility and designed in a fault-tolerant way, so that even if lockup or a fault occurs, the amount of energy is limited to safe levels. Being patient-connected, there is a high probability that oximeters and RGMs are used in a stack of other monitors, and therefore not only must they be hardened against interference, they must control their own emissions. Compatibility encompasses not being susceptible to, and not generating interference in, other ME equipment.

Powerful microprocessors have enabled complex software algorithms to see through the physiologic and environmental noise, both for managing alarm systems and for decision making. As the complexity rises, the ability to produce quality software requires integration between the engineer developing the algorithms and the clinicians specifying what physiologic condition the algorithms are meant to detect. Software with this degree of complexity is best developed in an organized, methodical manner that includes a documented development process, and one where the artifacts generated by the process reflect the decisions made. IEC 62304 (8) identifies life cycle processes appropriate for developing software-based medical devices.

Understanding a monitor's response time specification requires an understanding of what that response time represents. As with all physiological systems, the response to changes is not instantaneous but consists of a delay time and a rise time (e.g., as with a change in delivered inspired oxygen concentration and the resulting change in measured Spo_2 at a peripheral site such as the finger). Similarly, monitors have their own inherent response time. The response time of a monitor is typically a function of both hardware and software considerations and constraints. In oximeters, an insufficient response time might cause rapid short-lived hypoxic episodes to go undetected. An insufficient response time in a CO_2 monitor could result in a value closer to the average exhaled concentration and not the plateau being reported as an end-tidal value.

In a fluid-measurement monitor such as a RGM, delay time (sometimes called "lag" or "transit" time) depends on sampling flow rate, diameter and length of sampling tube, and sample viscosity. Delay time is negligible for nondiverting RGMs, whereas for diverting RGMs, it could be clinically relevant. ISO 21647 creates a single method for defining total system response time, the time from the step function change in gas levels at the sampling site to achieve 90% of a final gas reading, thus allowing performance comparison between monitors.

PROTECTIVE MEASURES—ALARMS AND LABELING

Understanding response time and detection time are essential for safely implementing alarms systems, since the total time to generate alarm signals is a function of both. The pulse oximeter and RGM standards detail methods for assessing response time. Alarm system response, including alarm signal generation, is an important feature for engineers to adequately explain, so that clinicians understand how to operate and interpret the alarm signals, especially as there might be multiple analysis engines operating in parallel. Both groups need to contribute to establish safe alarm limit defaults and alarm condition priorities. Clinicians need to establish clinically relevant alarm limits, and engineers need to insure that the alarm limits are realistic from the perspective of the ME equipment. For example, the default low Spo_2 alarm limit for pulse oximeters was decreased from 90% to 85% in the most recent version of ISO 9919 due in part to the trade-off between patient protection, false-positive alarm conditions, and ease of use (see rationale to subclause in AA.201.5.4 of ISO 9919). ISO 21647 notes that for each monitored respiratory gas, the monitor shall provide a means to detect alarm conditions with a minimum priority specified. The only high-priority alarm condition listed is for when the fraction of inspired O_2 is $<18\%$. This could be life-threatening and can be caused by a mechanical failure, since this occurrence is usually not the result of a clinical intervention. Alarm systems are a major category of risk control measures and have such importance that an entire standard, IEC 60601-1-8 (9), addresses their safe use.

Where a hazard cannot be designed out or protective measures devised to reduce risk to an acceptable level, the residual risk needs to be conveyed in labeling. Labeling must also explain the proper use of the equipment with an explanation of the accuracy, response time, and alarm. Placement and clarity of labeling is often the last thing to be addressed during

development, and therefore may suffer from a lack of human factor considerations (10).

A clinician should know the capabilities of the monitor being used; hence, the important performance characteristics should be reported in clear language and located in a place that is accessible. The accuracy, sensor specifications, patient population, instructions for use, warning, and contraindications are all important elements that must be in the labeling. If oximeter accuracy range could vary by population, selected monitoring site, or skin pigmentation, then this important information must be clearly indicated. If it is determined that there are limitations on the application time or the response time of the monitor, these should be reported in the labeling with sufficient detail that the clinician can understand how to make use of the monitor outside of ideal conditions.

A confusing labeling situation arises for reprocessed single-use sensors where both the original manufacturer and the reprocessor can have visible labels. It is essential that users understand that the performance of reprocessed sensors might be different from that of the original sensor. Reprocessors must demonstrate that they meet their performance specifications after the maximum stated number of cleaning cycles. Hence, there must be a way to track the number of cycles. The only way to do this is through labeling, placing the label where it has a chance of being read.

CONCLUSIONS

ME equipment for monitoring oxygenation, ventilation, or physiologic vital sign indicators of these processes are complex and have great potential for improving health care. However, this equipment must be properly designed from the start to be safe and effective. Manufacturers must pay attention to identifying appropriate hazardous situations and establishing effective risk control measures. This must involve both clinicians and engineers throughout the risk management activities in the product lifecycle. Regulators and standards writers blend the concerns and expertise of both engineers and clinicians to produce more refined, safe, and clinically useful assessment and assurance tools. A multidisciplinary team approach is an essential element of a safe medical device.

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Abstracts Presented at the International Symposium "Innovations and Applications of Monitoring Oxygenation and Ventilation" (ISIAMOV), Duke University, Durham, NC, March 15–17, 2007

Cerebral and Pulse Oximetry Monitoring of Newborns — Clinical Observations

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INTRODUCTION: Cerebral oximetry, which is based on near-infrared spectroscopy (NIRS) technology, is a non-invasive optical technique that offers continuous real-time monitoring of cerebral tissue oxygen saturation ($SctO_2$). $SctO_2$ represents the blood oxygen saturation in the microvasculature of brain tissue, which contains a mixture of arterial and venous blood, and reflects the balance between cerebral oxygen supply and demand. A cerebral oximeter (FORE-SIGHT™, CAS Medical Systems, Branford, CT USA) has been previously validated on neonatal patients during Extracorporeal Membrane Oxygenation (ECMO) (1,2). From the data collected in the validation study, we observed the relationship between cerebral oximetry and pulse oximetry measurements.

METHODS: After obtaining informed consent, we used the cerebral oximeter to monitor neonates undergoing veno-venous or veno-arterial ECMO. A specially designed neonatal sensor was attached to the subject's left or right forehead. Arterial oxygen saturation (SpO_2) data was collected from a Nellcor N-395 (Tyco/Nellcor, Pleasanton, CA USA) pulse oximeter with the sensor placed on the neonate's foot. For the study, cerebral oximetry and pulse oximetry data was collected every 3 seconds. Pre-ECMO surgical event markers were also recorded.

RESULTS: 30 subjects were studied with a total of >1200 hours of cerebral and pulse oximetry data collected. For the most part, cerebral oximeter $SctO_2$ and pulse oximeter SpO_2 closely correlated with each other. Typical SctO2 observed values were 65 to 90% during clinically stable conditions, with observed typical SpO_2 values of 88 to 100%. $SctO_2$ values tended to be 20–30% lower than SpO_2 because cerebral oximetry interrogates mostly venous blood in the microvasculature of the brain. During certain clinical situations, pulse oximetry was either less sensitive to brain oxygenation changes compared to $SctO_2$, or did not function reliably during low perfusion conditions such as circulatory arrest leading to the application of cardiopulmonary resuscitation (CPR). The case study shown in Fig. 1 is one example where pulse oximetry was intermittently functional, while cerebral oximetry continued to be reliable during CPR. Other cases show that during hyperemia or increased FiO_2, cerebral oximetry $SctO_2$ was sensitive to brain oxygenation changes while pulse oximetry was not able to measure changes because arterial oxygen saturation was at 100%.

CONCLUSION: Current use of real-time non-invasive pulse oximetry to monitor arterial blood oxygenation is often unreliable during low perfusion events, especially during circulatory arrest because of diminished or cessation of pulsatile blood flow. Also, pulse oximetry is not a direct indicator of brain oxygenation. Cerebral oximetry offers a direct method to measure cerebral saturation and potentially predict brain injury caused by an impaired balance between cerebral oxygen supply and demand. These results demonstrate the value of cerebral oximetry to monitor the effectiveness of CPR in situations where pulse oximetry is unreliable. Cerebral oximetry is a promising modality for bedside monitoring in the NICU and is complementary to pulse oximetry.

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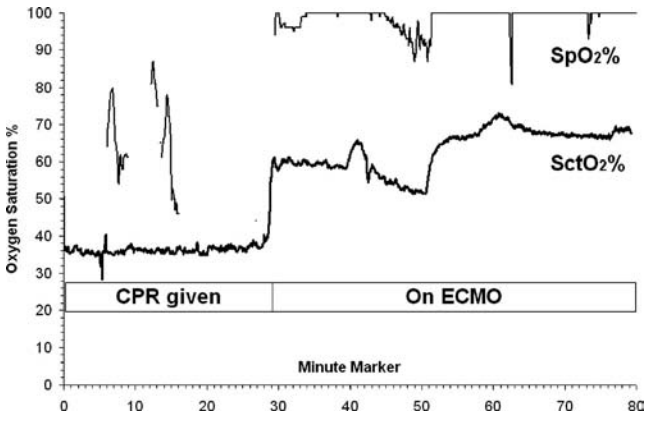

Photograph of the pediatric/neonatal esophageal pulse oximetry probe.

The Effect of Improper Pulse Oximetry Sensor Placement on Spo_2 Measurement Accuracy

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In clinical settings, the accuracy of pulse oximeter sensors is often presumed, even when the sensor is used "off-label" in alternative locations such as the ear, cheek, tongue, forehead, or nasal septum. Although Spo_2 data can often be obtained from

Disposable Sensors

	Max-A			LNOP-Adt			Oxy-Tip		7000A	
	Proper	Ear	Brow	Proper	Ear	Brow	Proper	Ear	Proper	Cheek
A	81.7	35.8	21.7	59.1	50.9	47.9	75.4	51.9	68.7	53.9
B	18.3	35.8	25.0	26.2	24.8	30.8	19.4	24.0	29.8	29.1
C	0.0	28.3	53.3	14.7	24.4	21.4	5.2	24.0	1.6	17.1
A_{RMS}	1.9	5.1	10.4	4.4	6.9	5.3	3.4	5.4	2.5	4.2

Reusable Sensors

	DS-100A		LNCS DSI		8000A	
	Proper	Sideways	Proper	Sideways	Proper	Sideways
A	79.8	55.1	60.7	54.7	45.2	32.9
B	18.7	22.6	28.2	20.9	39.7	31.0
C	1.6	22.2	11.1	24.4	15.1	36.0
A_{RMS}	2.1	5.3	3.7	5.4	4.1	5.4

All values given are in percentages.

these malpositioned sensors, to date, no studies have demonstrated whether such usage is accurate across the full range of saturation. This study compared the accuracy of malpositioned sensors with their properly placed counterparts, using a properly placed forehead sensor as reference (Nellcor Max Fast sensor, $A_{RMS} < 2.0$). Sensors examined in this study focused on disposable digit sensors (Nellcor Max-A, Masimo LNOP-Adt, Nonin 7000A, and the Datex Ohmeda Oxy-Tip) placed on the ear, forehead, or cheek, and reusable sensors (Nellcor DS100-A, Masimo LNCS, Nonin 8000A) placed sideways on a digit. The protocol used to assess Spo_2 across a range of saturations followed standard methodology recommended by ISO 9919. Results demonstrate that regardless of sensor make or type, Spo_2 reading accuracy is no longer maintained when sensors are malpositioned. This is increasingly obvious at lower saturation levels. In a χ^2 analysis of the number of readings within 2% Spo_2 compared with the reference sensor readings (A), between 2% and 5% (B), and greater than 5% (C), every malpositioned sensor had more readings in the B and C category than their properly placed counterparts ($P < 0.001$). The increase in A_{RMS} for all sensors was statistically significant when sensors were malpositioned ($P < 0.05$), with the exception of the Masimo LNOP-Adt ($P = 0.059$). The results from the present study highlight the importance of placing the sensors properly, especially in patients at risk of desaturations.

Pulse Oximeter Sensor Accuracy

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SUMMARY: Pulse oximetry is used worldwide every day and is often influential in clinical decisions. Brave talk about leading edge medical technology gives the impression of thoroughly reliable systems, completely compliant with regulatory requirements.

This is a misleading picture. It is as if pulse oximeter sensors are an embarrassing detail that has been overlooked. Pulse oximeter system accuracy is very dependent on sensor accuracy. Sensor accuracy is dependant on the spectral properties of the sensor being the same as those used during the clinical trials. All too often, this is not the case.

One thousand and eight sensors from 36 hospitals were surveyed. Thirty percent of these sensors were a cause for concern. Seventeen percent of the sensors surveyed had wavelength errors with corresponding SATs value errors capable of compromising patient safety.

PURPOSE: To investigate the implications of variations in pulse oximeter sensor optical characteristics on patient safety.

METHOD: A specialized spectrometer was used to determine the wavelength errors in pulse oximeter sensors. A wavelength error is defined as the difference between the expected wavelengths and the observed wavelengths.

The effect of wavelength errors on the calculated SATs value that would be displayed on the monitor was calculated at patient SAT values of 97%, 90%, 80%, and 70%.

The data were obtained from sensors either in use or held as spares in hospitals. The sensors included both disposable and reusable sensors from most manufacturers including both Original Equipment Manufacturers and Third Party Manufacturers.

RESULTS: One thousand and eight sensors were studied from 36 hospitals. Sensors with circuit faults and faulty optical components were noted, and accuracy data only taken from apparently functional sensors. Thirteen percent of the sensors had circuit faults. Seventeen percent of the sensors were apparently functional, but had SATs value errors of 4% or more.

DISCUSSION: When making accuracy claims the manufacturer has to allow for not only the biological variability between patients, but also any systematic errors introduced by variations in the sensor spectral properties. Often quoted accuracy claims for pulse oximetry allow for biological variability with little room for sensor-related systematic bias. In plain words, sensors of the same type, when used on the same person, should all read the same. However, in practice, they do not all read the same.

Only 14% of the sensors surveyed had no error, thus leaving 86% with errors of some sort. Seventeen percent of the sensors surveyed had SATs value errors of 4% or more. This is a systematic error with no component for biological variability, and such an error results in the pulse oximeter system failing to work as the manufacturer claims, and increases the risk of an adverse incident.

High-reading sensors can result in oxygen therapy being deferred or not given. Low-reading sensors can result in excessive oxygen therapy being given. Inappropriate oxygen therapy can lead to outcomes ranging from metabolic disturbances to death.

Changes in users expectations are putting greater demands on pulse oximetry. Some claim that new generation pulse oximeters can help reduce the incidence of ROP, but this is only if the accuracy of the sensors can be guaranteed. More patients are being treated while in hypoxia, large errors at low SATs compromise patient safety. The progress of many patients is recorded by monitoring trends in SATs values by spot checks. The value of this data depends on minimal variability between sensors.

Some believe that CE marking and FDA clearance are guarantees of sensor accuracy, but this belief is unfounded. In practice, mismatches between sensor spectral properties and the R curve in the monitor are putting patients at risk from the perils of excessive or insufficient oxygen therapy.

CONCLUSION: The accuracy of a pulse oximeter system is very dependant on the accuracy of the sensor. The accuracy of the sensor is largely dependant on the optical characteristics of the sensor matching the R curve in the monitor.

Not all sensors match the R curve in the monitor that they are used with. The data shows that variations in sensor spectral properties result in pulse oximeters not functioning as the manufacturers claim. Within the 36 hospitals surveyed, 30% of the sensors surveyed had unacceptable faults, including 17% of sensors with SATs errors of sufficient magnitude to compromise patient safety. Clinicians have come to rely on pulse oximeters. In good faith, judgments are based on the data they give.

The reliability of the data is very dependant on the accuracy of the sensor. If it is not known that the LEDs in the pulse oximeter sensor are within specification, every clinical decision made that is based on the data is without foundation.

Estimation of Pulse Oximetry Safety-Levels for Patients with Nail Polish Applied

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BACKGROUND: Nail polish of dark colors has repeatedly been reported to interfere with pulse oximetry (1,2) readings. Therefore, readings may deviate from the gold standard co-oximetry leading to a risk for unnoticed hypoxia. The aim of this study was to estimate three different pulse oximetry safety levels for critically ill patients with black, purple, or blue nail polish applied.

MATERIALS AND METHODS: After approval of the local ethics committee and guardian approval, three different nail polishes (black, purple, and blue) were applied standardized in two layers on finger nails in 50 critically ill and mechanically ventilated patients of an intensive care unit (ICU). Oxygen saturation was determined simultaneously by pulse oximetry (SpO_2; Siemens SC1281, Siemens Medical Electronics, Danvers, USA) and co-oximetry (SaO_2; Radiometer Copenhagen ABL System 625, Brønshøj, Denmark). The safety levels for each color were determined by graphical analysis of the correlation between SaO_2 (x-axis) and SpO_2 (y-axis) as previously suggested by Seguin et al. [3]. The safety-level (i.e. the SpO_2 needed) to guarantee a SaO_2 of 96% was determined on the basis of an error probability of $\alpha = 5\%$.

RESULTS: 50 patients (19 female, 31 male) with an age of 59 ± 14 years participated. Mean SaO_2 (97.8 ± 1.3%) correlated well with mean SpO_2 (97.5 ± 2.2%, n.s.) at the natural nail. Bias was calculated as $\Delta S = +1.6 \pm 3.0\%$ for the black, $\Delta S = +1.2 \pm 2.6\%$ for purple, and $\Delta S = +1.1 \pm 3.5\%$ for blue nail polish. To guarantee a SaO_2 of 96% with an accepted error probability of $\alpha = 5\%$, the following SpO_2 values were graphically determined: $SpO_2 = 99\%$ if black nail polish was present, $SpO_2 = 98\%$ for purple, and $SpO_2 = 100\%$ for blue nail polish.

CONCLUSION: If nail polish is not removed, compliance of these safety levels (SpO_2: black 99%, purple 98%, and blue 100%) during intensive care routine treatment may help to reduce the incidence of unrecognized hypoxic episodes (e.g. $SaO_2 < 96\%$).

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Accuracy and Precision of Three Different Methods to Determine Pco_2 ($Paco_2$ Versus $Petco_2$ Versus $P_{tc}co_2$) During Interhospital Ground Transport of Critically Ill and Ventilated Adults

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INTRODUCTION: Interhospital transportation (IHT) of critically ill and mechanically ventilated patients represents a common, yet difficult, problem. Three different methods to determine Pco_2 during IHT are feasible in clinical routine: arterial blood gas analysis with mobile analyzers ($Paco_2$), end-tidal ($Petco_2$), and transcutaneous ($P_{tc}co_2$) measurement. The aim of the present study was to compare accuracy and precision of these three methods simultaneously in critically ill and ventilated adults during IHT.

METHODS: Patients scheduled for interhospital transport were investigated after written informed consent and approval of the local ethics committee in this prospective clinical study. Pco_2 was determined five times in each patient during the transport simultaneously by 1) arterial blood gas analysis ($PAco_2$ [IRMA], IRMA®, mobile analyzer, Diametrics Inc., St. Paul, USA), 2) end-tidal measurements with capnography ($Petco_2$, Propaq 106 EL Monitor, Protocol Systems Inc., Beaverton, USA), and 3) transcutaneous measurements ($p_{tc}co_2$, Radiometer Copenhagen, Brønshøj, Denmark). The data obtained during transportation were compared with an in-hospital reference measurement ($PAco_2$ [ABL625]) as gold standard (ABL 625, Radiometer Copenhagen, Brønshøj, Denmark). For statistical analysis of accuracy (bias, systematic error) and precision (random error) a Bland-Altman analysis was performed. A $P < 0.05$ was considered statistically significant.

RESULTS: One hundred and seventy data sets ($Paco_2$ [ABL625], $Paco_2$ [IRMA], $Petco_2$, $P_{tc}co_2$) were obtained in 34 patients (61 ± 16 yr old; 19 male, 15 female). The mean $Paco_2$ [ABL625] was 43.2 ± 8.8 mm Hg ranging from 24.9 to 72.4 mm Hg. Bland-Altman analysis revealed a bias and precision of −0.6 ± 2.5 mm Hg for the IRMA device ($P > 0.05$) and −0.6 ± 7.5 mm Hg for the transcutaneous measurement ($P > 0.05$) compared with the gold standard. The end-tidal bias and precision (−5.3 ± 6.1 mm Hg) differed significantly ($P < 0.003$) when compared with the in-hospital reference measurement ($Paco_2$ [ABL625]).

CONCLUSIONS: During IHT $Paco_2$ [IRMA] and $P_{tc}co_2$ provide the best accuracy when compared with the reference measurement. For patients who either require a tight control of Pco_2 or endured lengthy transportation, capnography alongside arterial blood gases or the transcutaneous measurement of Pco_2 could be useful.

Artificial Acrylic Finger Nails May Interfere with Pulse Oximetry

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INTRODUCTION: Pulse oximetry is the most common technique to monitor oxygen saturation (Spo_2) during anesthesiology, emergency medical treatment, and intensive care therapy. However, intermittent cooximetry with a hemoximeter (Sao_2) is still the "gold standard" to validate Spo_2 measurements. Numerous influencing factors have been reported to interfere with pulse oximetry and may result in faulty readings. One of these factors is artificial acrylic finger nails. Clinical data on this topic are not sufficiently published.

METHODS: After approval of the local ethics committee and informed consent, a prospective clinical study in mechanically ventilated and critically ill patients of an intensive care unit (ICU) was performed. Patients were randomly assigned to either group S (S = Siemens pulse oximeter) or group P (P = Philips pulse oximeter) before the measurements. Spo_2 was determined in each patient three times alternately in standard ($^{N}Spo_2$) and sideways position at the natural nail ($^{N90}Spo_2$). For the reference measurements, oxygen saturation was measured by means of cooximetry (Sao_2). Thereafter, Spo_2 was obtained at the acrylic finger nail in the same way ($^{A}Spo_2$ and $^{A90}Spo_2$). Bias was calculated as [Delta]S = $^{N}Spo_2 - Sao_2$ and [Delta]S = $^{A}Spo_2 - Sao_2$. Accuracy (mean difference) and precision (standard deviation) were used to determine the measurement discrepancy. For statistical analysis, the *t*-test was used. $P < 0.05$ was considered significant.

RESULTS: A total of $n = 46$ critically ill and mechanically ventilated patients (14 female and 32 male) were investigated. Accuracy and precision without acrylic nails applied were comparable to Sao_2 in both groups (group S: [Delta]S = −0.7% ± 2.51%, group P: [Delta]S = +0.6% ± 2.77%; each n.s. and $n = 23$). With acrylic nails applied a bias of [Delta]S = −1.1% ± 3.14% for group S ($P = 0.005$) and a bias of [Delta]S = +0.8% ± 3.04% for group P (n.s.) was calculated.

CONCLUSION: This is the first clinical study analyzing pulse oximetry accuracy and precision in patients with artificial acrylic finger nails present. Acrylic finger nails may impair the measurement of oxygen saturation depending on the pulse oximeter used and may cause significant inaccuracy. Hence, removal of artificial acrylic finger nails may be helpful to assure an accurate and precise measurement with pulse oximetry.

Optimizing Conditions for Acquiring and Understanding Oxygenation Data in a Clinical Setting

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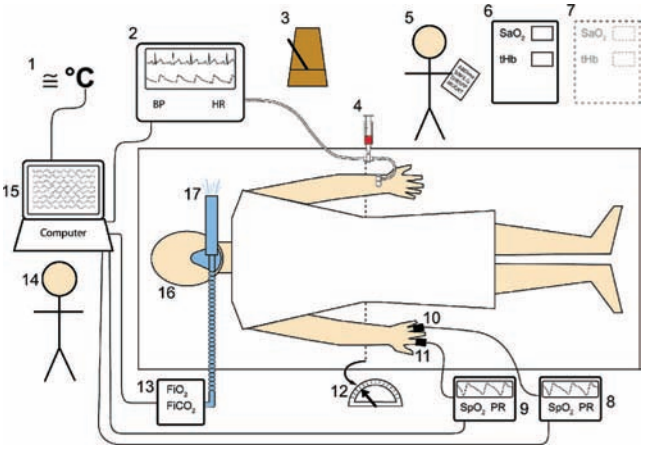
INTRODUCTION: Two large, nondevice industry-sponsored studies suggest that pulse oximeters lack the accuracy claimed by their manufacturers for Spo_2 values in neonates and adults during routine clinical use (1,2). Typically, manufacturers calibrate pulse



The laboratory used by device manufacturers to calibrate and test performance of pulse oximeters is dissimilar from the clinical setting in many aspects: 1. Ambient temperature is finely controlled and often computer captured. 2. Same blood pressure and ECG waveform with heart rate monitor. Output is computer captured. 3. Metronome or equivalent audible timer to assist test subject with regular breathing. 4. Radial artery catheter on hand opposite that being tested with PO sensors. 5. Consistent analysis technician who assures ideal conditions for environment and test subject. 6. CO-oximeter in close proximity. This device is carefully maintained. 7. Second CO-oximeter is often present to corroborate results. 8. Device history is known and meets manufacturer's maintenance recommendations. Output is computer captured. 9. Same as item 10. 10. Pulse oximeter sensor is shielded from ambient light and from light of adjacent sensor(s). Same PO sensor for entire study. 11. Reference (prequalified, predicate device) pulse oximeter to evaluate if test site is performing appropriately. 12. Position of the test subject is purposely maintained for the study design. 13. System for calibrated and finite mixing of hypoxic and normocarbic gases. 14. Independent technician who assures oxygenation and normocarbia plateaus conditions with correct data acquisition. 15. Data acquisition of reference and pulse oximeter under test occurs with input from other pertinent aspects (wired paths). 16. Well perfused, conscious, and cooperative test subject. 17. Passive breathing circuit without positive pressure assisted inspiration or PEEP/CPAP.

Optimizing Comparison of a CO-Oximetry Sao_2 Value with Pulse Oximetry (PO) Spo_2 Values in Clinical Care

User action	Rationale
Expose the stopcock used for sampling arterial blood but avoid noise, touch and movement of bedding.	Exposure to cold, noise or touch can startle patient with change of their resting state, respiratory and cardiac rhythmicity.
Observe the PO sensor to be certain it is well aligned, secured and generating maximize signal quality.	A misaligned or loose sensor will reduce PO performance and signal quality.
• Before sampling blood, assure stability of patient's data condition [Spo_2 (±2%) and PR (±3 bpm) values] for at least 90 s. • Note anything during blood sampling that is likely to adversely affect the Spo_2 and pulse rate values (e.g., change in breathing, change in supplemental oxygen or mechanical ventilator setting).	Stability in PO data is essential for Sao_2 comparison. Typically, the circulatory path is traversed by a RBC in 60 s so allowing 90 s of stable Spo_2 should assure a matching Sao_2. Also, equilibrium is required to overcome monitor averaging time.
Assure complete removal of the non-blood fluid (e.g., flush solution) from the arterial catheter and sampling line for at least two times the dead space volume.	The specimen must contain solely arterial blood. Hemodilution and various nonblood fluids (e.g., hyperalimentation and lipids) can alter Sao_2 accuracy.
Sample blood slowly.	Exposing whole blood to vacuum can outgas CO_2 and O_2 thereby altering $Paco_2$ and Pao_2, hence Sao_2.
Express any air bubbles and cap the syringe.	Air is a contaminant and can alter $Paco_2$ and Pao_2, hence Sao_2.
Agitate specimen just before analysis.	A homogenous blood sample is ideal.
Analyze the blood within 2 min of sampling.	RBC metabolism continues in a stored specimen, thereby altering pH, $Paco_2$ and Pao_2, hence Sao_2. This is especially true in leukocytosis, where the Po_2 can drop more than 50% within 2 min of sampling.
Visualize and record the bedside ECG HR, Spo_2 and PR values.	Timely data capture reduces error.
Record Sao_2 findings, using the functional not fractional Sao_2 value.	Functional Sao_2 is reference for Spo_2.

oximeters by using data from healthy adults. These test subjects are trained to breathe hypoxic gas mixtures to achieve oxygenation plateaus. Reference material is available to assist the clinician in their quest to optimize conditions for acquiring and understanding oxygenation data (3–8).

METHODS: The following table was distilled from the reference material and categorizes the user action and rationale affecting various aspects of device performance. The figure that follows illustrates the idealized laboratory conditions for comparison of blood gas and pulse oximetry data.

CONCLUSION: The accuracy claims by manufacturers of pulse oximeters are better than the performance experienced in clinical care. Trained users with improved device instructions that better care for the instrumentation can improve correlation of blood gas and pulse oximetry data in the clinical setting.

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Shortcomings for Achieving Laboratory Quality Blood Gas and Pulse Oximetry Data in the Clinical Setting

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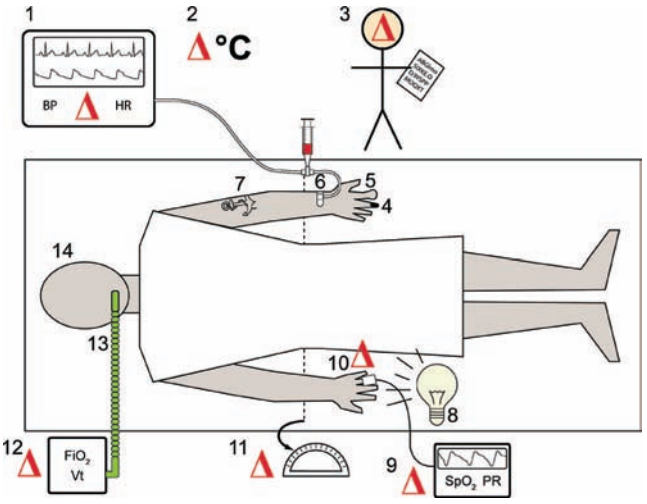
INTRODUCTION: Data suggest that pulse oximeters in routine clinical use lack the accuracy claimed for Spo_2 values by their manufacturers for adults and neonates. A metaanalysis of 74 studies on adults revealed a dramatic difference in Spo_2 to Sao_2 correlation between "healthy adult volunteers" and "critically ill/ICU patients," $r = 0.96$ and 0.76, respectively (1). In clinical use (i.e., not laboratory testing), use of 21 oximeter models had a range of Spo_2 to Sao_2 correlation from 0.99 to 0.59, with variability found even within the same model. A multicenter study of acutely ill neonates compared nearly 32,000 data sets of Sao_2 to Spo_2 values collected during routine care (2). Multiple brands of CO-oximeters (ABL, Beyer and Instrumentation Laboratory) and pulse oximeters (Datex-Ohmeda, Masimo, Nellcor and Spacelabs) were used. None of the pulse oximeters provided a consistent bias or precision of Spo_2 values across the range of Sao_2 of 70%–100%. The authors' concluded, pending improvement in Spo_2 accuracy, adjustments to supplemental oxygen and ventilator settings in the NICU patient "must be based on and reevaluated by arterial blood analysis." Clearly, there is more "noise" than "signal" with pulse oximetry data in clinical environs.



The clinical setting often contains many facets that adversely affect pulse oximeter performance: 1. Often various blood pressure and ECG monitors are used during test period (or no monitor is used). 2. Ambient and patient temperature is uncontrolled and often not measured at time of study. 3. Various caregivers with individual techniques for assessing patient, documenting data, and sampling blood. 4. Nail polish or acrylic nails may exist. 5. Digital clubbing may exist. 6. Artery catheter may be on same hand being tested with PO sensor or could be in site not matching oxygenation status of PO. 7. Tattoos may exist at PO sensor site. 8. Varying levels of contaminating, ambient light may exist. 9. Various models of pulse oximeters often used and performance altering oximeter settings often changed (e.g., averaging time). 10. Varying sensor sites and sensors often used. Sensor is often unshielded from ambient light. 11. Patient position is routinely changed to match care requirements. 12. Source of mechanical or assisted ventilation, the setting for which frequently change to match care requirements. 13. Varying levels of CPAP or positive pressure assisted inspiration with PEEP. 14. Patient is often poorly perfused or perfusion varies during test period. Patient is often unconscious and noncooperative. Hemoglobin concentration may also vary during test period (and may not be recorded with oximetry data).

Comparing Sao_2 to Spo_2 Data in Acute Care Versus that from Controlled Laboratory Conditions (Effects in Parentheses)

ICU or other site of acute care	Controlled laboratory conditions
Variables affecting the oxyhemoglobin disassociation curve are common (shifted by chemistry [pH, CO_2, 2,3-DPG, fetal Hb, or dyshemoglobins] and physics [temperature])	Variables that affect the oxyhemoglobin disassociation curve are rare and purposely avoided
Patient's hemoglobin is: • Likely variable in the same subject over testing period • Values often low (<11 g/dL), especially in preterm (Anemia adversely affects Spo_2 accuracy)	Hemoglobin level stable and normal for adults (13–15 g/dL)
Dyshemoglobins are likely and variable in the same subject over testing period, e.g., methemoglobinemia can occur with nitric oxide (NO) therapy. (COHb and MetHb are known to adversely affect Spo_2 accuracy)	Dyshemoglobins unlikely
Arterial blood pressure is likely variable in the same subject over testing period; moreover, neonatal BP is comparatively lower than adults (64/38 ± 6 mm Hg) and even lower in preterms (50/28 ± 3 mm Hg); often labile too (hypoperfusion can adversely affect Spo_2 accuracy)	Arterial blood pressure is typically 120/80 ± 15 mm Hg and stable
Variable ambient temperature can change peripheral perfusion (changing peripheral perfusion can alter Spo_2 performance)	Ambient temperature controlled with test site heated to maximize pulse strength
Oxygenation values unstable due to subject's pathology and care interventions such that many variables can enter the test environment and subject: 1. Heart, lung or vascular issues as detailed below: • Heart: Dramatic changes in heart rate and/or stroke volume are frequent and likely during testing. • Lung: Apnea, hypopnea, bronchospasm and secretions are likely during testing. Additionally, most test subjects are on supplemental oxygen, which can be associated with swings in FIo_2 thereby Spo_2, e.g., crying or apnea/hypopnea cycles with a nasal oxygen cannula. • Vascular: Circulatory shunts can complicate correlation of Sao_2 to Spo_2 values; radial and umbilical artery catheterization will compromise downstream flow, which can impair Spo_2 performance. • Swings in response to heart, lung or vascular-targeted drugs are likely over the course of care. 2. Test subject activity is unmanaged such that even waiting for an "ideal" test period can be wasted by unanticipated patient activity. 3. Post blood sampling dynamics can adversely affect Spo_2 stability and synchrony (e.g., airway care). 4. Bright light sources are often needed for care, e.g., bili-lights. (light and motion artifact can adversely affect Spo_2 accuracy)	Expected that Spo_2 values are stable and predictable without which blood draws for Sao_2 measurements are not taken. 1. Test subjects are healthy without therapeutic interventions during the study such that Spo_2 value stability is likely, owing solely to controlling FIo_2. Indeed, pre-screening removes subjects with lung, heart and circulatory pathology (e.g., lack of pharmokinetics during testing). 2. Test subjects are experienced and compliant such that: • Breathing pattern uniform • No innate motion
Arterial blood draw is: • Initiated for clinical care • Infrequent (often hours between samples) • Single sample (Matched Sao_2 to Spo_2 values is essential for accurate comparison)	Arterial blood draw is: • For reference data • Taken at will • Multiple and in close time proximity • Postponed if conditions unstable

Continued

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ICU or other site of acute care	Controlled laboratory conditions
Secondary PO sensor in proximity to that under test not possible d/t lack of space and, if placed, there is likelihood of crosstalk between sensors (optical crosstalk between PO sensor contaminates PO values)	2nd qualified PO sensor in close proximity to sensor under test is routine; optical shielding between sensor readily achieved
A patient is unlikely to cover range but rather a small area in the overall range (local bias can shift Spo_2 accuracy from that claimed by manufacturer)	A given adult subject is likely to have a constant bias over the range of measure
Sensor position may be compromised by: • Nonideal sensor placement (due to innately small surface area and presence of space occupying materials like IV/IA arm boards); also, cannot readjust sensor prior to blood draw as the patient's state is disturbed and remains such for a lengthy period thereafter • Sensor age (causes reduced adhesion and clouded detector window) • Age of site use (skin opacifies from adhesives) • Subject position will likely vary during study period (e.g., lateral, prone, supine), each results in unique ventilation/perfusion ratios in the lungs; may lay on limb, which can slow speed and degree of perfusion (sensor condition can adversely affect PO performance)	• Many uncompromised sensor sites • Sensor sites are optimized with fresh preparation, fresh sensor and preselection of most ideal site (e.g., maximum perfusion index) • Same site on each test subject is used for entire study • Test subjects are kept in the same position, which is to ease arterial line access and optimize lung function, i.e., semi-fowlers
Spo_2 values vary at individual, uncontrolled points • No reference to stage taking a blood sample • Lack of blood sampling rigor, e.g., draw speed, draw volume, air and heparin volume, stopcock position, time before analysis, capping of syringe opening, agitation before analysis (avoid sedimentation or false tHb), and transcription (technique inconsistency causes data variability)	Points of Spo_2 stability are expected • Spo_2 values controlled against 2° reference with discrete plateaus • Single technician draws, transports and injects sample into CO-oximeter and transcribes the results
Chemical and dilutional contamination, e.g., base therapy, hyperal., interlipids (hemodilution and various non-blood fluids can alter Sao_2 accuracy)	Only saline infusion into arterial catheter
CO-oximetry data accuracy worsened due to: • Multiple personnel (both for sampling and analysis) • Multiple brand and model instruments (the integrity of CO-oximetry data can be affected by above variables)	CO-oximeter performance consistent with single technician, often using multiple CO-oximeters so that the data is averaged (with opportunity to discard outlier data)
Limited room so manual data recording common (open to transcription, stability and synchrony induced errors)	Computerized data collection routine with real-time and post-processing benefits)
Layers of variables: environment, patient, caregivers, supplies, reference device (multivariable setting with great chance for errors)	Focus of limiting variables in setting, test subject, staff, supplies and reference device
Nail polish, acrylic nails, digital clubbing, and tattoos are commonplace (these variables in the sensor optical path can adversely affect Spo_2 accuracy)	During recruiting, can disqualify or correct subjects with items of optical contamination

METHODS: The following table summarizes the differences in the clinical and laboratory settings known to affect device performance. The figure that follows illustrates the sources of "noise " found in clinical care with blood gas and pulse oximetry data.

CONCLUSION: Pulse oximeter manufacturer accuracy claims are better than those found in clinical studies. This discrepancy is likely owing to data of healthy volunteers with skilled technicians in controlled laboratory conditions versus clinicians collecting patient data in the chaos of clinical care. Knowing and compensating for the device and setting limitations should improve correlation of blood gas and pulse oximetry data for clinicians.

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Uses of Software Interfaces in the Study of Commercial Medical Devices

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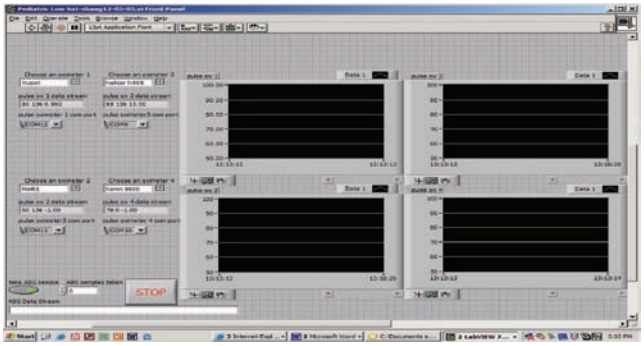
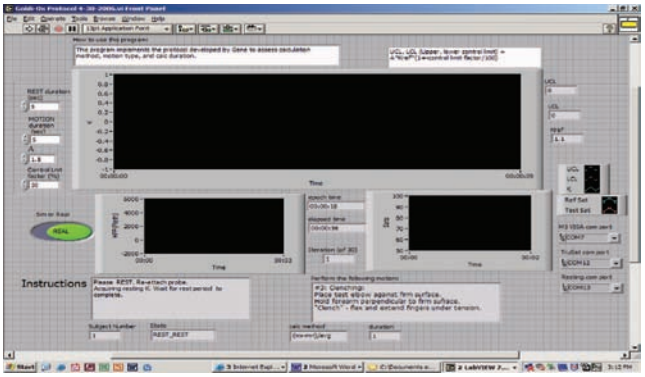
INTRODUCTION: Advances in technology have allowed for rapid development of new and improved clinical monitoring devices. As important as the swift development of technology is the expeditious development of methods for analyzing and evaluating the accuracy and safety of this technology. An important secondary goal for these analytical methods and data collection systems is to integrate patient data into usable and meaningful displays in order that scientist and clinicians can evaluate multiple systems or patients at a glance.

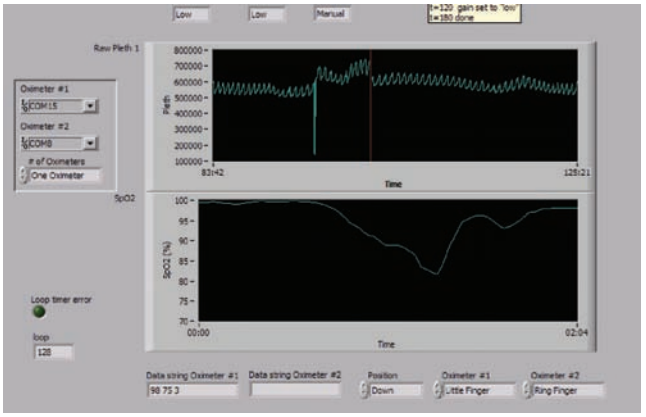
One highly useful tool for collecting and analyzing data is LabVIEW®, an object-oriented language that allows for the creation of virtual instruments. These programs are Graphical User Interfaces that the researcher can manipulate to modify the program



Front panel of pediatric low-saturation study virtual instrument.



Front panel of motion study virtual instrument.



Time-coupled plethysmographic and saturation data.

options and displays. The "front panel" also allows for simultaneous visual display of real-time data from multiple devices. LabVIEW is also optimized for the control, interface, and automation of instrumentation. Further, the nature of the LabVIEW environment lends itself to the real-time processing of data, which can also be simultaneously displayed with the raw data. Raw and processed data can then be recorded in Excel ® spreadsheets for additional analysis and evaluation.

Another attractive feature of this language is the ease with which applications can be developed. Prototypes can be built using the using the prepackaged tools or a custom hierarchy can be developed. The "dataflow" nature of the environment makes it ideal for a "test-as-you-go" approach to application development. This type of development makes accurate development easy and requires very little troubleshooting in the final stages of prototyping (1).

A particular area of interest is in the collection of pulse oximetry data. Currently our group has several ongoing studies that would be impossible without the aid of LabVIEW. One of these studies is the characterization of motion artifact via plethysmographic signals (2). Another study is underway to compare the accuracy of pulse oximeters in pediatric patients with low saturations (3). Three particular challenges that LabVIEW allows these studies to address are time correlation of data, integration of multiple streaming data sources, and the comparison of data from different types of devices. The pediatric study requires up to four time-stamped data streams collected in parallel. The data are time correlated for precision data analysis. Figure 1 below shows the front panel used in this experimental setup.

The motion artifact study uses even more of LabVIEW's resources. The protocol calls for the collection, processing, and display of real-time, raw plethysmographic data. This data streams considerably faster and must retain its temporal signature; otherwise, it will not be useful.

At the same time, as shown in Figure 2, there is considerable feedback into the front panel of the program. This allows for considerable runtime functionality in the program, all while live data are being collected, displayed, and analyzed. Figure 3 shows the collection of live plethysmographic data and oxygen saturation data. Precision timing in LabVIEW allows for the analysis of this plethysmographic waveform when oxygen saturation is low.

The examples presented here focus on leveraging the technology provided by LabVIEW to improve the ability of scientists to collect reliable data and perform data collection and analysis techniques previously impossible with traditional mean of hand and automated data collection systems. Our simple experiments hardly begin to scratch the surface of the capabilities of this resource. As long as devices are capable of generating digital output, and have some sort of data output port, LabVIEW should be considered as a viable and valuable tool in scientific research.

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Motion Resistance of Pulse Oximeters: A Clinically Informative Test?

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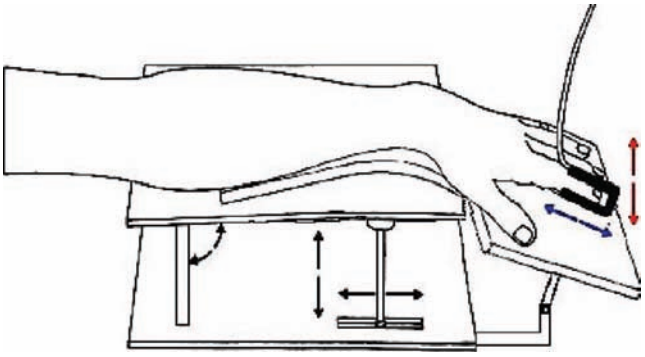
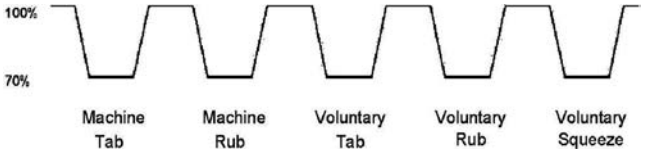
Spontaneous movements of the patients hand or fingers as well as irritations via the bed or the operation table may lead to faulty or absent pulse oximeter (PO) readings due to the motion artifacts. This effect of motion may be fatal on the detection of rapid changes of arterial saturation. At present, there is no FDA-approved standardized procedure to test pulse oximeters with respect to motion resistance (1). The aims of the present study were 1) to evaluate the performance of the test protocol and 2) to observe the reliability and functionality of pulse oximeters with respect to the presence of manually and mechanically generated motion artifacts and induced desaturation.

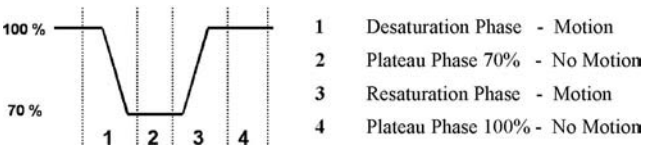


Motion table.

Squeezing movement.



Desaturation sequences with associated movement categories.



Sections of one movement category.

A_{rms} %Spo_2 for Each Subject and Movement Category

Subject	Machine tap	Machine rub	Volunteer tap	Volunteer rub	Volunteer squeeze
1	4.04	4.43	6.03	5.02	6.34
2	4.50	6.56	6.73	6.34	6.07
3	3.15	3.00	3.59	6.65	4.39
4	4.93	5.74	6.59	10.96	10.43

METHODS: Motion was generated both mechanically via a table (Fig. 1) and manually by the subject. The movements are categorized in three patterns: scratching, tapping, and squeezing. Scratching and tapping are performed both manually and mechanically, whereas squeezing is done only by the subject by compressing a soft ball (Fig. 2).

With the approval of the Ethics Committee of the Medical University of Luebeck and written informed consent, four healthy volunteers (2 male, 2 female, 26–34 yr of age) participated in the study. Hypoxemic state was induced by breathing a mixture of air with reduced oxygen content through a tight fitting face mask. Vital parameters such as ECG, inspiratory and expiratory oxygen, and carbon dioxide content were continuously monitored.

We used the left hand as the reference hand, which remained motionless, and the volunteer's right hand as the test hand, which was subjected to motion. The hands were positioned at heart level and identical sensors and pulse oximeters were applied to the same fingers on the test hand and the reference hand. To maintain the position of the sensor during motion, adhesive digit sensors were used and an opaque cover to avoid interference with ambient light.

PROCEDURE: For each motion category, we established a rapid de- and resaturation procedure (Fig. 3).

Before and after each de- or resaturation period, there was 1 min on a stable plateau—-controlled with the reference PO—-for test PO signal recording, followed by a 2-min break without movement (detailed protocol Fig. 4). The subject's oxygen saturation started at 100% and was rapidly decreased to approximately 70% and held constant for about 4 min. Then, resaturation was induced back to 100% and held constant for about 4 min. This program was repeated five times with the scheduled motion categories.

RESULTS: Data of both reference oximeters and those under test have been recorded and analyzed continuously. All pulse oximeters tested showed similar patterns in curve progression. The test PO randomly lost track of signal and showed zero reading. This artifact caused a false alarm to be displayed. For the test versus the control Spo_2, the accuracy A_{rms} (root-mean-square of the differences) was calculated (see the following table for details). A_{rms} increased when the subject performed active movements.

DISCUSSION: The evaluation of pulse oximeter performance under conditions of motion and hypoxemic state has been demonstrated. The protocol presented introduces both the motion and the rapid change of saturation under standardized and repeatable conditions.

REFERENCE

1. ISO 9919:2005 International Organization for Standardization. March 2005

Pilot Study in Neonatal and Pediatric Oesophageal Pulse Oximetry

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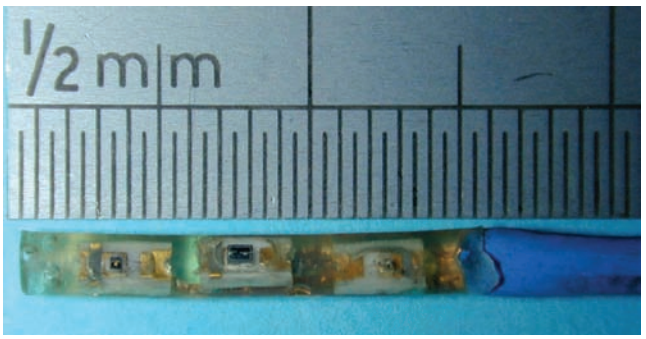
PURPOSE: The primary objective of this proof-of-concept pilot study was to investigate the feasibility of detecting photoplethysmographic (PPG) signals and estimating blood oxygen saturation (Spo_2) values from the esophagus of children and neonates. This vital measurement can be impossible to obtain at times when it is most needed during septic shock, circulatory collapse, or cardiac arrest.

METHODS: *Instrumentation.* A miniaturized reflectance esophageal pulse oximeter probe was constructed comprising one infrared and one red



Photograph of the pediatric/neonatal esophageal pulse oximetry probe.

surface mount emitter (880 and 655 nm) and a surface mount photodetector mounted between the emitters (Fig. 1). The probe was designed to be small enough to slide down the lumen of a plastic transparent disposable size 12F (external diameter of 3.8 mm) nasogastric tube. A processing system was constructed to preprocess, record, and display esophageal PPG signals and estimate Spo_2 values on a laptop computer. PPG signals were analyzed by a virtual instrument (VI) implemented in *LabView*. Algorithms (1) were also developed in the VI for the online estimation of esophageal Spo_2.

Patients and Measurements. Local research ethics committee approval was obtained for this proof-of-concept pilot study. Five neonates (3 M, 2 F) were studied on the neonatal and pediatric intensive care units. The age range (days), ± SD was (5 to 1398, ±606) and the weight range (kg), ± SD was (1.9 to 10.0, ±3.3). The esophageal probe was advanced gently through the mouth to a maximum depth of 15 cm from the lips. The babies were all mechanically ventilated and adequately sedated. The probe was withdrawn slowly until PPG signals with high signal-to-noise ratio could be obtained. The probe was then left at this depth for the duration of the study for approximately 10 min, and PPG traces and derived Spo_2 values were recorded. During the esophageal measurements, Spo_2 values from a commercial toe pulse oximeter (Philips, Merlin CMS Monitors, Reigate, UK) were also recorded for comparison.

RESULTS: Good quality PPG signals from the esophagus were recorded in all patients. The measured effective signal-to-noise ratio was always better than 40 dB at the output of the system. A total of 48 pairs of Spo_2 values from the five patients were used to compare the esophageal and the commercial toe pulse oximeters. The limits of agreement between the esophageal Spo_2 results and those from the commercial toe pulse oximeter, were calculated using the *between-method differences* analysis outlined by Bland and Altman (2). The bias, estimated by the mean difference (d) was −0.34% and the standard deviation (s) was 0.67%. The limits of agreement for the Spo_2 data (commercial toe and esophageal) were:

$$d - 2s = -0.34 - (2^* - 0.67) = 1.0\%$$

$$d + 2s = -0.34 + (2^* - 0.67) = -1.70\%$$

CONCLUSIONS: A new reflectance esophageal pulse oximetry probe and an isolated processing system have been developed, which allow measurements to be made within the esophagus of neonates and children. In this preliminary study, it has been shown that good quality esophageal PPG signals with large amplitudes can be measured within the esophagus of neonates. This appears to be the first report of PPG signals from the esophagus of neonates. In a direct comparison between the esophageal and commercial pulse oximeters, using Bland and Altman analysis, the preliminary Spo_2 results from the two instruments were in good agreement. This study suggests that the esophagus can be used as an alternative site for Spo_2 monitoring in neonatal and pediatric patients and encourages more extensive and rigorous clinical trials.

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Photoplethysmography and Blood Oxygen Saturation During Blood Pressure Cuff-Induced Hypoperfusion

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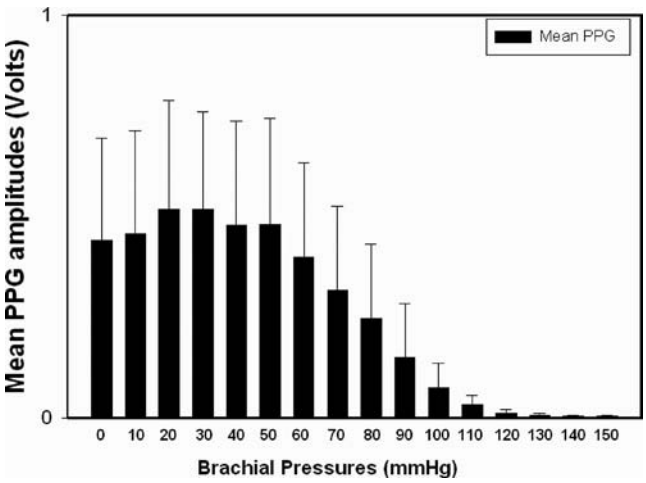
PURPOSE: The primary aim of this pilot study was to investigate the morphology and amplitude of the photoplethysmographic (PPG) signal and its effect on blood oxygen saturation (Spo_2) under controlled vasoconstriction.

METHODS: A reflectance finger PPG/Spo_2 probe was constructed comprising two infrared and red emitters and a photodetector. A processing system was also developed (1,2) to detect and preprocess the PPG signals. Blood oxygen saturation values were also obtained using a commercial transmittance finger pulse oximeter (*Diascope 2 VISMO;* S&W Medico Teknik). PPG traces from the custom-made pulse oximeter and Spo_2 traces from the commercial pulse oximeter were digitized by a 16-bit data acquisition card. A virtual instrument (VI) implemented in LabView was used for the displaying and storing of all acquired signals. The digitized signals were analyzed offline in Matlab 6.5.

The institutional Ethics Committee approved this study, and all subjects gave written consent for participation. Fourteen healthy volunteers, mean age, ± SD (28 ± 5.2) participated in this study. Volunteers were told to rest comfortably in the supine position in an examination table for 3 min to obtain a stable hemodynamic period. The cuff of the sphygmomanometer was then placed on the left arm at the level of the brachial artery. The custom-made reflectance finger PPG/Spo_2 probe was placed on the index finger of the left hand and the commercial pulse oximeter was placed on the ring finger of the same hand. Hypoperfusion was induced by gradually occluding the brachial artery at increments of 10 mm Hg (10–15 s per pressure increment). During the gradual hypoperfusion process, all parameters were monitored and recorded.

RESULTS: Measurable PPG traces were obtained in all volunteers in all pressures taken before complete arterial occlusion where the finger PPG signals ceased due to no blood flow to the finger. Figure 1 gives the mean (SD) of the ac infrared PPG amplitudes at the different pressure increments. A Kruskal–Wallis one way analysis of variance on ranks test showed that there were statistically significant differences between the ac PPGs in the low pressures (0–80 mm Hg) than those in the upper pressures (90–150 mm Hg) at both wavelengths. The Spo_2 values from both pulse oximeters were decreased gradually as the cuff pressure increased. With the systematic occlusion of the brachial artery, the volume of blood reaching the finger was decreased and that was obvious from the changes in the amplitude of the ac PPG signal from the custom-made finger probe. In many occasions, the commercial pulse oximeter failed to give any saturation values after the release of the cuff for approximately 100 s, where the custom-made probe was able to estimate Spo_2 immediately after the cuff was released.



Mean infrared ac PPG amplitudes (SD) at various pressure increments.

DISCUSSION AND CONCLUSION: Good quality PPG signals with large amplitudes were measured at all induced pressures before complete occlusion of the brachial artery in all volunteers. During hypoperfusion, the amplitude of the PPG signals were decreased gradually to the point that were not visible. The decrease in the amplitude of the PPG signals correlated well with the decrease in Spo_2. This is in agreement with the physiological phenomenon that suggests that during arterial vessel stenosis the volume of blood decreases with a direct effect on Spo_2 values measured at a vascular site downstream from the stenosis. The custom-made finger pulse oximetry was found to be more sensitive to Spo_2 changes during induced hypoperfusion when compared with the commercial pulse oximetry. Additional clinical studies, in a group of patients with peripheral vascular disease, are suggested to investigate such a phenomenon further.

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Accuracy of a Novel Bioacoustic Sensor in Adult Postoperative Patients with and Without Lung Disease

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INTRODUCTION: Monitoring respiration of spontaneously breathing patients with chronic obstructive lung disease(COPD) is a concern in a variety of clinical areas including the operating room, postanesthesia care unit (PACU), and on the general care wards. The respiratory status of these patients requires careful vigilance, as they may demonstrate particular sensitivity to analgesics and postoperative pain medications. Most current devices to monitor respiration are limited because they require either a cannula system positioned in line with airflow to detect respiration or impedance pneumography, which is prone to missing obstructive apnea (1). A novel bioacoustic sensor for continuously monitoring respiration has been developed. We evaluated the accuracy of the prototype sensor in adult postoperative patients with and without COPD in the postanesthesia care unit.

METHODS: After institutional IRB approval and informed consent, 30 postoperative patients, 19 without lung disease and 11 with COPD, upon arrival to the PACU, were enrolled in this study. All patients were monitored in the standard fashion; in addition, a nasal cannula was placed, secured with tape, and connected to a BCI capnometer (SIMS, Waukesha, WI). An adhesive bioacoustic sensor connected to a breathing frequency monitor prototype (Masimo Corp., Irvine, CA) was applied to the patient's neck just lateral to the cricoid cartilage. Both the capnometer and the bioacoustic monitor were connected to a computer for continuous data recording and subsequent data analysis. The accuracy of the new acoustic sensor and the capnometer were compared with a reference respiratory rate from a manual scoring system. Bias, precision, and A_{RMS} were calculated in the usual fashion, as either bioacoustic sensor-reference or capnometer-reference.

RESULTS: All data are expressed as mean ± SD. Nineteen patients without lung disease (age = 54.6 ± 20.7 yr) and 11 patients with COPD (age = 51.1 ± 9.8 yr) were enrolled. Duration of monitoring time in PACU was 58.2 ± 36.9 min. Respiratory rate varied 3–28 bpm during this time. For the patients without lung disease, the resultant bias, precision, and A_{RMS} for the capnometer compared with the reference value was −0.48, 2.20, and 2.25, and bioacoustic sensor compared with the reference sensor was 0.04, 2.43, and 2.43, respectively. For the patients with COPD, the resultant bias, precision, and A_{RMS} for the capnometer compared with the reference value was −0.31, 2.46, and 2.48, and bioacoustic sensor compared with the reference sensor was 0.01, 2.76, and 2.76, respectively.

CONCLUSION: The new prototype bioacoustic respiratory sensor demonstrates accuracy for respiratory rate monitoring as good as capnometry in PACU patients with and without COPD. This data suggests the new bioacoustic sensor may provide a system at least as accurate as capnometry for monitoring respiration in spontaneously breathing patients with and without COPD. This device offers multiple benefits over existing devices and has a potential to improve monitoring of both healthy patients and patients with lung disease in a general care setting.

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Continuous Noninvasive Measurement of Hemoglobin via Pulse CO-oximetry

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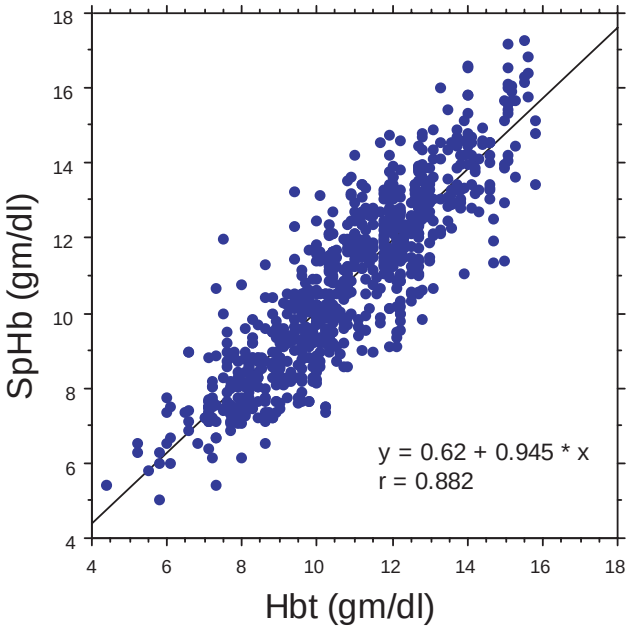
BACKGROUND: New advances in pulse oximetry technology have led to the development of multiwavelength pulse CO-oximeters designed to measure multiple physiologic parameters. The utilization of multiple wavelengths has led to the development of a prototype pulse CO-oximeter that allows for measurement of continuous hemoglobin concentration (SpHb). This study examines this device's ability to measure continuous SpHb and evaluates the accuracy compared with hemoglobin concentration (Hb) measured in a laboratory CO-oximeter.

METHODS: After IRB approval and informed consent, 30 patients scheduled to undergo surgery and 18 healthy volunteers undergoing a hemodilution protocol were enrolled in this ongoing study. Each subject was monitored with ASA standard monitors and a radial artery cannula. Three prototype SpHb sensors, optically isolated from each other, were attached to a data collection system (Masimo Inc., Irvine, CA). Routine anesthetic care of these patients was not altered. The hemodilution protocol consisted of withdrawal of 1 U of blood and replacement with 30 mL/kg of saline. Data were collected throughout the course of each surgery and during hemodilution. Arterial blood samples were analyzed by laboratory CO-oximeter (Radiometer ABL735), and the resulting Hb measurements were compared with the data collected from the corresponding SpHb readings. Regression analysis, bias, precision, and A_{RMS} were calculated.

RESULTS: Eight hundred and two data pairs were collected from a total of 48 subject. The mean (±SD) and range of Hb values were 10.7 (±2.2) and 4.4–15.8 g/dL, respectively. Bias, precision, and A_{RMS} were 0.03, 1.12, 1.12, respectively. The figure shows the correlation



between Hb and SpHb and the regression analysis. The *y* intercept is 0.62, the slope is 0.954, and the correlation coefficient is 0.882.

DISCUSSION: This device is the first device developed that can continuously and noninvasively measure hemoglobin concentration, in addition to the other common hemoglobin species, and therefore provides a significant expansion of existing physiologic monitoring technology. Rapid measurement of hemoglobin would be an extremely useful tool in many clinical scenarios. This technology in combination with methemoglobin and carboxyhemoglobin measurements should allow for significant advances inpatient care.

Pulse Oximeter Accuracy: Multiple-Laboratory Evaluation

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INTRODUCTION: Validating pulse oximeter saturation (Spo_2) accuracy requires comparison to the true arterial oxygen saturation (Sao_2) across the full specification range. Although methods are standardized (1), information comparing results among multiple laboratories is limited. We evaluated accuracy of five sensor/monitor configurations at three facilities.

METHODS: Independent data collection was performed at Nellcor's performance testing laboratory in Pleasanton, CA; Clinimark Laboratories, Golden, CO; and at the University of Lübeck, Lübeck, Germany.

Each facility used the same general methodology for testing as described by ISO 9919 (1). After their respective IRB approved protocols and informed consent, pulse oximeter Spo_2 readings obtained on healthy adult volunteers were compared to arterial blood Sao_2 assessed by CO-Oximetry over the range ≤70%–100% Sao_2 during normal perfusion and nonmotion conditions. Two manufacturers' systems were included (Nellcor *OxiMax® N-600™*, Nellcor, Pleasanton, CA; Masimo Radical®, Masimo Corporation, Irvine, CA). Each system was tested with multiple sensor designs (Table 1).

Digit sensor placement was rotated among subjects in a balanced design. Each subject had an indwelling arterial catheter for periodic sampling and was exposed to progressive stepwise hypoxic air/nitrogen mixtures to attain the specified saturation range. Stable Spo_2 levels were maintained to ensure tissues at the pulse oximetry sensor site were at the same Sao_2 as found at the radial artery sampling site.

Data Analysis. Computation spans were adjusted for data inclusion to provide a comparable data density over the lower (≤85%) and upper (>85%) Sao_2 ranges as suggested in ISO 9919. Accuracy (root-mean-square of the Spo_2 to Sao_2 differences, ARMS) was determined for each system. Occurrence of Spo_2-SaO2 > 4% over the range 70%–100% SaO_2 was compared with an expected 95% count of observations (consistent with an ARMS = 2%) using the Fisher's exact test to determine significance ($P < 0.05$).

Table 1. Tested Oximetry Systems

Monitor	Sensor	System
OxiMax N-600 (v1.1.2.0)	MAX-A adhesive digit sensor	A
	MAX-N adhesive digit sensor	B
	MAX-FAST® forehead sensor	C
Masimo Radical (v4.3.2.1)	LNOP®-Adt adhesive digit sensor	D
	LNOP®-Blue™ adhesive sensor	E

Table 2. Data Summary

	California	Germany	Colorado
Subjects	12	13	12
Computation Span	68%–99%	70%–97%	70%–100%
Stable Samples	227	793	239
≤85% / >85%	113/114	395/398	120/119
System	A_{RMS} (%SpO_2): Overall and ≤85%/>85%		
A	1.9	1.5	2.3
	2.2/1.15	1.6/ 1.3	2.8/1.7
B	1.8	1.6	2.2
	2.1/1.5	1.7/1.5	2.6/1.8
C	1.3	2.0	2.8*
	1.6/1.0	2.5/1.4	3.4/1.9
D	4.6*	3.0*	2.8*
	6.4/1.6	4.0/1.7	3.6/1.7
E	4.1*	2.7*	2.1
	5.6/1.4	3.5/1.4	2.6/1.5

*Observed A_{RMS} greater than 2%, $P < 0.05$.

RESULTS: Thirty-seven subjects spanning a range of age, gender, weight, and skin pigmentation were studied, with 1259 data pairs collected (Table 2). A, B, and C performed at the ≤2% A_{RMS} level in each California and Germany; Colorado results imply $A_{RMS} > 2\%$ with C data statistically significant ($P < 0.001$).

Systems D and E exceeded 2% A_{RMS} at all three facilities ($P < 0.001$ California/Germany; Colorado: $P = 0.012$ (D), E = N.S.). Accuracy for each system was better in the upper saturations than the lower 70%–85% Sao_2 span. System differences were greatest in the lower span, particularly as observed in California and Germany.

DISCUSSION: A_{RMS} differences between systems A, B, C, D, and E appear due primarily to bias in the lower span, though magnitude was laboratory-dependent. Possible residual differences between laboratory procedures may affect the local biases at the lower saturations. Relative system bias curves were consistent across labs, suggesting A_{RMS} differences may relate to the subjects, subject management, and/or blood sampling and analysis. Further investigation is indicated.

CONCLUSION: Spo_2 accuracy varies between pulse oximeter systems as independently observed at different laboratory facilities, particularly at low Sao_2. Specific A_{RMS} values differ across laboratories. LNOP, Blue, and Radical are trademarks of Masimo Corp. All other trademarks belong to Tyco Healthcare Group LP or an affiliate.

REFERENCE

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Dilatational Tracheostomy Using the KLEMM Tracheotomy Endoscope, a New Procedure for Percutaneous Dilatational Tracheostomy in Intensive Care Medicine

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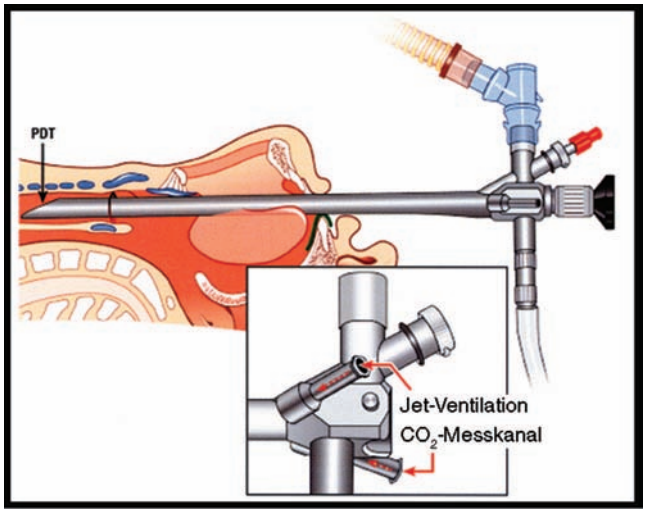
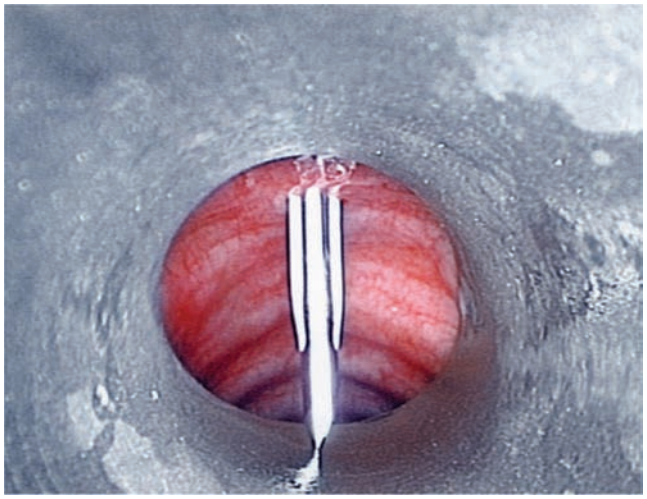
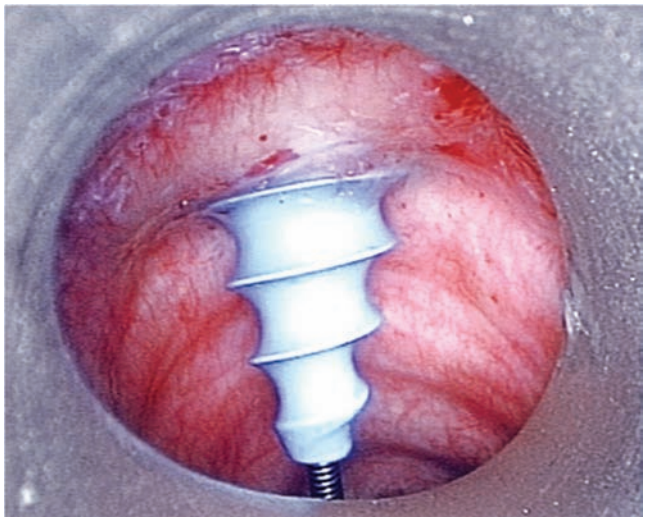
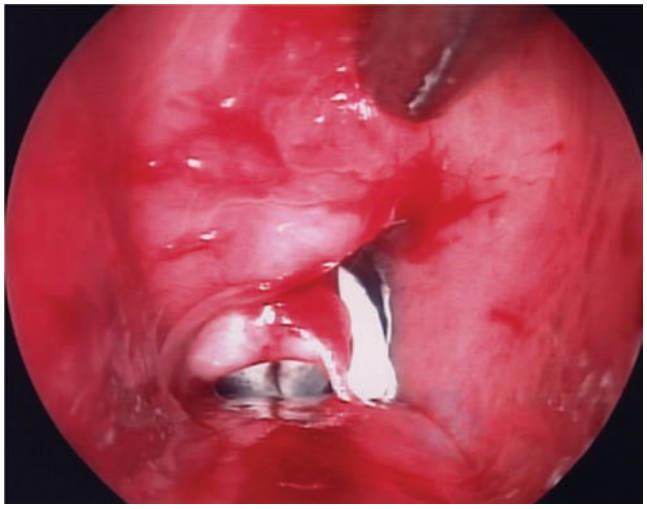
INTRODUCTION: There has been an unbroken trend toward percutaneous dilatational tracheostomy (PDT) in intensive care medicine. In Germany, approximately 23,000 PDTs are now performed each year in intensive care medicine, compared with 5000 open surgical tracheotomies (1). Observations to heavy perioperative complications of the PDT (posterior wall injuries, heavy bleeding, pneumothorax, tracheal ring fractures, tracheal stenosis, respiratory difficulties) demands an improved management of the PDT. For this







reason, the development of the tracheotomy endoscope was started (2). Injuries to the posterior tracheal wall are serious and potentially fatal complications of percutaneous tracheostomy. STEIN found a 7% incidence of injuries, 2% of which were perforating injuries that required invasive thoracic surgery (3). Dost and Koeser (4), reporting the results of a recent survey in Germany, documented six



posterior wall injuries and seven tracheoesophageal fistulas. In a review of the literature, Oeken et al. (5) found 40 severe posterior wall injuries and 28 cases of pneumothorax. Delank et al. (6) report on five post-PDT lesions requiring operative treatment. Stein (5) found an 18% incidence of cartilage fractures under endoscopic control, and he found 15 fractures in 21 cases that were autopsied after PDT. Frova and Quintel (7) report an 8% incidence of cartilage fractures using Percu Twist® screw. Ambesh et al. (8) cite a 30% incidence of tracheal ring fractures using PDT.

METHOD: The new tracheostomy endoscope (TED) is designed to help prevent serious complications in dilatational tracheotomies and facilitate their management (2). The method is based on the principle of ventilation laryngoscopy (VLS) described by Fabian and Brandt in 1964–1965 (9,10). The new endoscope (TED) has been specifically adapted to meet the requirements of percutaneous dilatational tracheotomies. It is fully compatible with all current techniques of PDT. The projecting posterior lip of the tracheotomy endoscope prevents inadvertent puncture of the posterior tracheal wall. The prismatic light deflector provides a maximum illumination. Optimal puncture site is marked by transillumination with a curved fiberoptic light carrier inserted through the endoscope. Different ventilation modes are possible with the tracheotomy endoscope: Jet ventilation via built-in jet channels and manual bag ventilation. The endoscope has a built-in CO_2 measurement channel. The endoscope is CE-certified (CE 0123).

RESULTS: Large blood vessels in the anterior part of the neck are clearly outlined by the transilluminating effect of the tracheotomy endoscope. Use of the tracheotomy endoscope eliminates the familiar problem of flexible endoscopes narrowing the lumen of endotracheal tube, making it necessary to interrupt the tracheotomy to optimize ventilation. This can be particularly troublesome in critical care patients with a small-diameter indwelling tube. Because flexible endoscopes are not suitable for either the visualization or treatment of heavy bleeding, a rigid endoscope during PDT allows blood removal with large-diameter suction tubes. Bleeding into the trachea can be safely controlled under good endoscopic vision using sturdy metal insulated suction cannula and coagulating tubes. Displaced cartilage fracture fragments can be immediately repositioned endoscopically, and smaller fragments or tissue debris can be removed. This eliminates the risk that displaced fragments may become epithelialized and narrow the tracheal lumen (2).

CONCLUSION: Experiences in clinical application and first results of a pilot study confirm positive expectations that tracheotomy endoscope increases the standard of safety in PDT.

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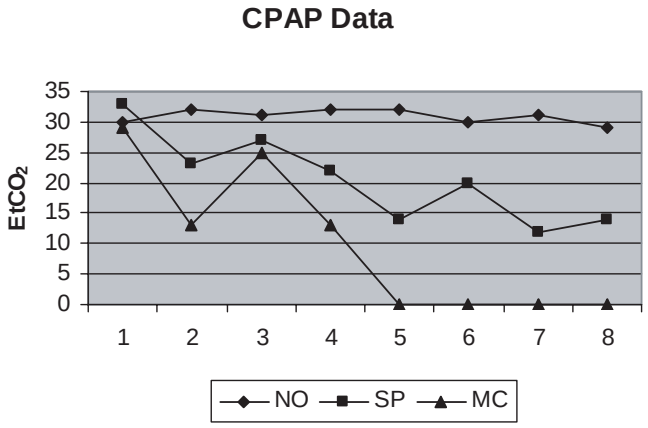
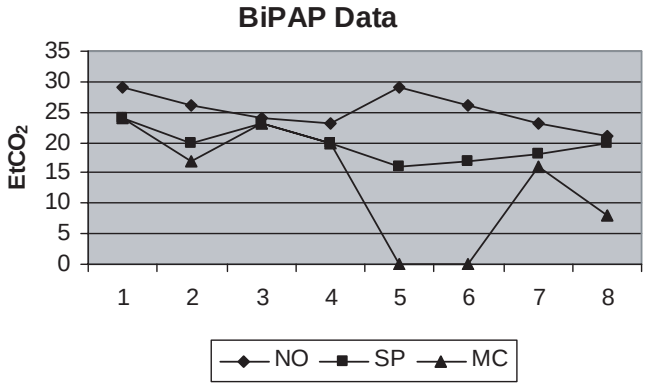
CPAP data

Mask type	FFNP	FFNP	FFNP	FFNP	FFEP	FFEP	FFEP	FFEP
CPAP level	5	5	10	10	5	5	10	10
PL	10	20	10	22	32	60	34	80
MV	7	5	7	6	6	6	6	6
$Etco_2$ NO	30	32	31	32	32	30	31	29
$Etco_2$ SP	33	23	27	22	14	20	12	14
$Etco_2$ MC	29	13	25	13	0	0	0	0

ST Data

Mask type	FFNP	FFNP	FFNP	FFNP	FFEP	FFEP	FFEP	FFEP
EPAP level	5	5	5	5	5	5	5	5
IPAP Level	10	10	15	15	10	10	15	15
PL	12	20	14	20	32	70	34	75
MV	9	10	12	15	7	10	13	13
$Etco_2$ NO	29	26	24	23	29	26	23	21
$Etco_2$ SP	24	20	23	20	16	17	18	20
$Etco_2$ MC	24	17	23	20	0	0	16	8





End-Tidal CO_2 Measurements with Noninvasive Ventilation

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STUDY OBJECTIVE: To understand the technical aspects of measuring end-tidal CO_2 ($Etco_2$) in the noninvasively ventilated (NIV) patient. A laboratory study was conducted to compare simultaneous $Etco_2$ data from three different sample sites with commonly used patient interfaces, NIV modes, and varying patient leak rates.

DESIGN: Minute ventilation (MV) and $Etco_2$ readings were collected simultaneously at three different sample sites with commonly used clinical pressure settings and modes. Two types of full-face masks were used: 1) no expiratory ports in the mask (FFNP) (Respironics), 2) expiratory ports in the mask (FFEP) (Fisher Paykel).

SETTING: Laboratory.

METHODS: $Etco_2$ measurements were collected using Microcap (Oridion) microstream capnographs. Sample sites were 1) nasal/oral sample line (NO) (Smart CapnoLine H Plus, Oridion), 2) sample port (SP) on the mask, and 3) sample line at the ventilator tubing and mask connection (MC) point. A noninvasive ventilator (BiPAP Vision, Respironics) was used to deliver commonly used settings in CPAP and spontaneous timed (ST) modes. The three $Etco_2$ site readings were taken at two different patient leak (PL) levels for each mode and pressure settings.

RESULTS: The data revealed there were significant variations in $Etco_2$ results at the different sample sites. The nasal/oral (NO) sample site was very consistent throughout all settings and patient leak rates.

In the ST mode the nasal/oral (NO) sample site was more reliable for appropriate $Etco_2$ readings at different ventilator settings and patient leaks.

CONCLUSION: The sampling site for CO_2 in NIV can greatly influence the reliability of the $Etco_2$ value. The nasal/oral (NO) sample line proved to be the most reliable in trending $Etco_2$ with different ventilator modes, settings, and leak rates in the normal patient.

Making Pain Management Safer Using Capnography: Three cases

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INTRODUCTION: Approximately 98,000 patients die annually because of medical errors. Risk factors include patient controlled analgesia (PCA) by proxy (1). Capnography, monitoring of ventilation, may reduce risk factors. Our postoperative patient management during PCA includes the use of noninvasive capnography.

METHODS: Three patients where monitored postoperatively using pulse oximetry (Spo_2) and end-tidal carbon dioxide ($Etco_2$), capnography, as part of that experience. Alarm limits were set per hospital protocol. Clinicians were alerted to respiratory depression when those alarms were activated.

RESULTS: All patients experienced respiratory compromise. Patients were determined to have impending respiratory compromise by $Etco_2$ before alert by the Spo_2 alarm conditions being activated. Patient 1 was evaluated as having respiratory depression due to previously unrecognized obstruction sleep apnea, secondary to obesity with an elevated $Etco_2$ of 74 and normal (90% or greater) Spo_2. Patient was treated and referred to the sleep lab for further diagnostics. Patient 2 was noted to have medication induced respiratory depression with a normal Spo_2 and decreasing respiratory rate, $Etco_2$ alarm occurred at 8 bpm and appropriate intervention was taken. Patient 3 was noted to have a no breath alarm via $Etco_2$ with normal Spo_2 and determined to have OSA with a subsequent referral to the sleep laboratory for further evaluation.

DISCUSSION: $Etco_2$ is the first indicator of respiratory depression in all patients in the series. $Etco_2$ alarms activated before Spo_2 alarms. Undiagnosed OSA was prevalent in these patients receiving postoperative analgesia for pain management. One patient required direct control of analgesia whereupon respiratory patterns returned to acceptable levels. All three patients experienced respiratory compromise, with normal Spo_2. These dysfunctions may have gone unrecognized or progressed to a more serious level without the use of capnography to monitor ventilation.

CONCLUSION: Reliance on Spo_2 as the primary indicator of respiratory status may not be adequate for patients at risk during PCA. Capnography is a measurement of ventilation and in this series gave advance notice of impending respiratory demise. Elimination of carbon dioxide is a function of ventilation and should be considered a primary monitoring tool of respiratory function. In this series, all PCA patients experienced a positive benefit through the incorporation of real time measurement of $Etco_2$.

Parameters and Range

Parameter	ctHb (g/L)	sO_2 (%)	T (°C)	pH-value
Range	50–200	50–100	37 ± 2	6.8–7.4

Noninvasive Measurement of Hemoglobin Concentration

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INTRODUCTION: A continuous and noninvasive measurement of critical parameters of whole blood such as oxygen saturation (sO_2) and hemoglobin concentration (ctHb) are of great advantage in clinical monitoring. At present, hemoglobin concentration is measured invasively, a time-consuming procedure that allows no real time measurement of ctHb.

Based on photometric analysis of optical determination of parameters in whole blood, a photometric device (PMD) has been developed, which allows an exact, noninvasive online ctHb and sO_2 measurement. The sensor is designed to measure at the finger site and in a tube. This device is applicable in clinical areas where blood is taken from the body via a drainage system and in the near future for application on patients noninvasively.

To determine the influence of sO_2, temperature (T), and the pH-value on ctHb progression an *in vitro* model was developed to demonstrate the correlation of invasively and noninvasively measured data of ctHb.

METHODS: The spectrum of whole blood in the visible and near infrared range is dominated by the absorption of hemoglobin, its derivatives and plasma. The principle the PMD uses is based on wavelength selective light absorption of whole blood. The device contains five-time multiplexed pulsed lasers diodes of different wavelengths (670, 808, 905, 980, and 1310 nm). The laser light is guided via fiber optics and a custom-built optic to the sensor head, which is designed to fit the tube. After the light interacts with the blood the transmitted signal is analyzed and the absorption coefficients of sO_2 and ctHb are calculated (1,2).

By measuring at wavelength $\lambda_k, k = 1, \ldots, K$ the values R_k are obtained, which satisfy the equation

$$(R_1, \ldots, R_K)^T = A(x_1, x_2, x_3)^T$$

with

$$A = \begin{pmatrix} \mu_{a,1}^{HbO_2} & \mu_{a,1}^{Hb} & \mu_{a,1}^{Plasma} \\ \vdots & \vdots & \vdots \\ \mu_{a,K}^{HbO_2} & \mu_{a,K}^{Hb} & \mu_{a,K}^{Plasma} \end{pmatrix} \quad \text{and} \quad (x_1, x_2, x_3)$$

$$= \Delta vr(HS_{o_2}, H(1 - S_{o_2}), 1 - H)$$

The elements of the matrix A are the absorption coefficients of oxygenated and deoxygenated hemoglobin in the erythrocytes as well as in plasma of whole blood at wavelength λ_k. The hemoglobin concentration can be obtained by solving the above linear equation.

The sensor was attached to a flexible silicone tube with a defined outer diameter of 0.17 in. The PMD has been verified in a hemodynamic model driven by a roller pump, which allows variation of blood parameters. A continuously moved blood bag served as a reservoir for the mixture of blood and plasma of a defined ratio to adjust ctHb. The integrated oxygenator allows a variation of the degree of oxygen saturation and the blood temperature (Table 1). Blood probes were sampled near the sensor and analyzed by a blood gas analyzer (ABL 725, Radiometer Copenhagen; Denmark).

Test Results

Modus	Samples	A_{rms}	SDR
AC	30	5.81	6.97
DC	40	3.06	4.29

The model allows a simulation of a steady (DC modus) and a pulsatile blood flow (AC modus) while the parameters to be measured have been changed separately or simultaneously. Tests were performed for both modes where sO_2 was changed and ctHb decreased. The precision as the standard deviation of the residuals (SDR) and the accuracy A_{rms} (root-mean-square difference between measured and reference values) for the ctHb were calculated.

RESULTS: Oxygen saturation was varied on the claimed ctHb levels and *vice versa* with this *in vitro* model. Although the temperature was held constant, the change of the pH-value led to no further effect on the measurements of sO_2 and ctHb. Based on the signal extraction, the measured values in the DC modus exhibit a lower variance than in the AC modus (Table 2).

DISCUSSION: The PMD seems to be able to follow the hemoglobin concentrations in a tube noninvasively in the AC and DC modus.

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Indirect Calorimetry System Based on Luminescence Quenching On-Airway Oxygen Sensor

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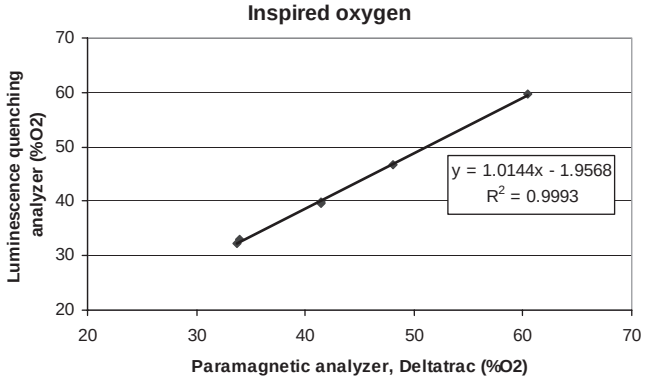
INTRODUCTION: We evaluated an indirect calorimetry system that uses an on-airway oxygen sensor based on the photoluminescence quenching principle.

Indirect calorimetry calculates metabolic rate and calorie consumption from directly measured oxygen uptake (VO_2) and carbon dioxide production (VCO_2). These systems measure the difference in volume or inspired and expired O_2 and CO_2 in respiratory gases. Most indirect calorimetry systems designed for use in critical care use sampling paramagnetic oxygen analyzers. Side sampling introduces challenges including signal alignment with the flow measurement, sampling tube occlusion and others.

METHODS: We used a patient simulator based on propane combustion to model oxygen uptake (VO_2) and CO_2 production (VCO_2). We compared the VCO_2, VO_2, and respiratory quotient as measured by the on-airway system with the standard paramagnetic oxygen sensor type metabolic analyzer (Deltatrac, Datex, Helsinki, Finland). The respiratory quotient (RQ) is the ratio of CO_2 production to oxygen consumption. Because the simulator burns propane gas, we know that the true respiratory quotient (RQ) should always be 0.6. On the basis of earlier studies (1), we assumed that the VCO_2 measurements for both systems were accurate. We then calculated the true reference VO_2 for each setting from the measured VCO_2 and the known RQ.

We ventilated the patient simulator using a Siemens 900C ventilator at two simulated metabolic rates using three inspired O_2 (FIO_2) levels at each simulated metabolic rate. The measured VO_2



and VCO_2 should have been the same at each simulated metabolic rate regardless of the inspired oxygen concentration. The measurements (FIO_2, VCO_2, and VO_2) were recorded as they were reported in real time. FIO_2, VO_2, and VCO_2 were recorded and compared for both monitors. The VO_2 results were also compared to the ideal VO_2 measurement calculated using the measured VCO_2 and the known RQ of 0.6.

RESULTS: The average difference in CO_2 production between the two systems was 0.5 ± 3.9 mL/min. The average percent difference was 0.3% ± 2.8%. The data plot below shows that the inspired oxygen (FIO_2) measurements correlated well (r^2 = 0.999). The average oxygen consumption (VO_2) error for the Deltatrac monitor was 23 ± 50 mL/min (5.8% ± 13.9%). The average error for the on-airway, luminescence quenching system was −13 ± 2.5 mL/min (−5.4% ± 1.3%).

The VO_2 measurement error using the on-airway system was consistently small across all inspired oxygen levels. The Deltatrac system showed a definite correlation between percent measurement error and the inspired oxygen concentration. Melendez et al. (2) found that the Deltatrac tends to measure VO_2 too high when the FIO_2 is increased.

CONCLUSION: Accurate measurement of oxygen consumption is one of the most challenging applications of respiratory oxygen monitoring. Our data shows that an on-airway oxygen analyzer based on luminescence quenching can be applied to provide accurate oxygen uptake measurements.

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Preliminary Evaluation of a Fiber Optic Cerebral Oximetry System in Patients Undergoing Neurosurgery

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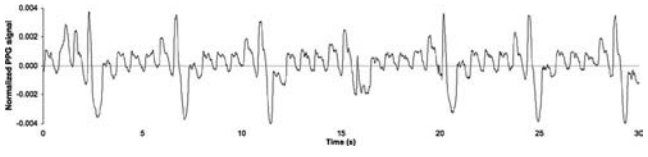
INTRODUCTION: Management of patients after major neurosurgical procedures, particularly in the days after traumatic head injury, aims to prevent secondary damage. Raised intracranial pressure (ICP) due to swelling of the brain can reduce blood flow and can lead to compromised delivery of oxygen to the brain tissue (1). For many years, management of patients at serious risk of raised intracranial pressure has included intracranial pressure monitoring via a cranial bolt inserted into a burr hole drilled through the skull (2). We have developed an optical fiber probe, which may be inserted via a cranial bolt, allowing oxygen saturation measurements to be made from the blood vessels within the brain tissue. A preliminary study was undertaken to determine whether photoplethysmographic (PPG) signals could be obtained from the brain tissue and to determine the optimal optical fiber characteristics and depth of penetration of the fibers into the brain.

METHODS: The probe consists of two silica optical fibers with a core diameter of 400 μm and a numerical aperture (NA) of 0.39. Each fiber is terminated at one end with an SMA connector and the other end is cut and polished flat. The instrumentation is housed in a metal box containing: red (660 nm) and infrared (850 nm) emitters, a PIN photodiode photodetector, a battery power supply, and a simple signal processing circuit. The signals for each of the two wavelengths are recorded and stored on a notebook computer using a LabVIEW-based data acquisition system (3).

This study was approved by the local Research Ethics Committee (Investigational Review Board) and patients' written informed consent was sought before the study. Patients who required cranial bolts as part of their routine neurosurgical care were recruited. After induction of anesthesia, the cranial bolt was inserted by the neurosurgeon. The fibers were inserted via the bolt, 5 mm into the brain and PPG signals recorded for 4 min. The fibers were then removed and the surgery resumed.

RESULTS: To date, five patients have been studied. Signals were successfully obtained at both wavelengths for all five patients, and 0.39 NA fibers performed better than 0.22 NA fibers. Figure 1 shows a sample of the infrared ac PPG waveform recorded from one patient. The PPG signals consisted of variations in intensity consistent with the cardiac frequency. In some patients, the PPG signal was modulated by a periodic signal of very large amplitude occurring at the respiratory frequency. This signal was thought to be caused by the ventilator-induced pressure changes in the cerebral circulation.

DISCUSSION: We have shown that good quality red and near-infrared PPG signals could be obtained directly from human brain tissue using a fiber optic probe. The 0.39 NA optical fibers and 5 mm depth of penetration appear appropriate for signal acquisition. This proof-of-concept study warrants further evaluation of the PPG brain probe to establish whether signal quality can be maintained for a clinically relevant monitoring period, and to correlate this method with other observations.



Infrared ac-filtered normalized PPG signals recorded from the brain tissue via a cranial bolt, with pulse rate 80 bpm, and superimposed ventilation artifact at 13 ventilations per minute.

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Pulse Oxigraphy: A Noncontact Imaging Approach

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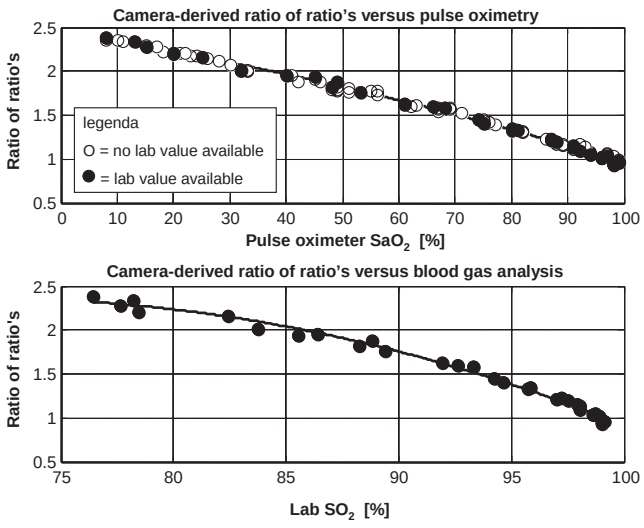
BACKGROUND: After its invention in 1974 by Aoyagi, pulse oximetry rapidly became an important vital monitoring sign. In medical history, each vital monitoring sign (i.e., heart rate, respiratory rate, temperature, blood pressure, and arterial oxygen saturation) considerably increased insights in normal and pathological physiology.

As the word "insight" illustrates, human perception matches better with images than numbers (thermography, e.g., helps understanding temperature household).



Likewise, viewing tissue oxygenation images might offer added value compared with "single point" pulse oximetry. Hence, we conceived a noncontact optical method to visualize arterial oxygen saturation distribution. It is based upon pixel-to-pixel matched camera movies in three spectral bands (660, 810, and 940 nm). For all three wavelengths, position-dependent photoplethysmograms are calculated. Then, applying the ratio-of-ratios method to the 660 and 940 nm signals, oxygen saturation levels are assigned to these positions. The images obtained at the 810 nm isobestic wavelength contain no oxygen information. They do, however, contain all artifacts like reflections, shadows, etc., which facilitates application as a reference. We describe an overview of our work in relation to this Spo_2-imaging concept.

METHODS:

A. With a monochrome CMOS-camera with apochromatic lens and 3λ-LED-ringlight (100 LEDs λ^{-1}), we acquired *in vivo* movies (duration 57 s; 13.7 frames per second) at three wavelengths while simultaneously recording ECG, respiration, and pulse oximeter pleth-wave (Nellcor N200). Movies were processed by dividing each image frame into discrete regions of interest (ROIs) averaging 10×10 raw pixels each. For each ROI, pulsatile variation over time was assigned to a matrix of 3072 ROI-pixel time traces with individual Fourier spectra.
B. Using the same camera and ringlight, *in vitro* camera-derived results ($n = 116$, 3 blood pools, ≥9 oxygenation setpoints/pool, and 4 heart rates/setpoint) were obtained from a heart-lung machine perfused phantom's central region (placed at 22 cm distance in a light-tight enclosure) and, using a third-order least-squares spline approximation fit, were compared with reflectance-mode pulse oximetry (Nellcor N200, $n = 116$) as well as with laboratory analysis (Radiometer ABL725, $n = 29$, 3 blood pools and ≥9 setpoints per pool).

RESULTS:

A. Fourier spectra of all three wavelengths showed that camera-derived signals matched well with the respiration reference signal peak as well as with the fundamental heartbeat frequency and its first harmonic. Pulse-oximeter plethysmograms showed a large DC-offset but no distinct respiration-matched peak.
B. Camera-derived results showed monotone and reproducible relations with pulse oximetry and laboratory values. However, pulse oximeter readings decreased about a factor 4 steeper than laboratory values when lowering the saturation setpoint. Therefore, the horizontal scales in Figures 1A and B differ.

CONCLUSIONS:

A. *In vivo* camera-derived photoplethysmograms at the wavelengths required for our concept could be derived, but with insufficient signal-to-noise ratio to calculate oxygen saturation.
B. *In vitro* camera-results demonstrate the feasibility of the pulse oxigraphic principle.

Capnography During Sleep Apnea Using a Novel Mainstream Capnometer

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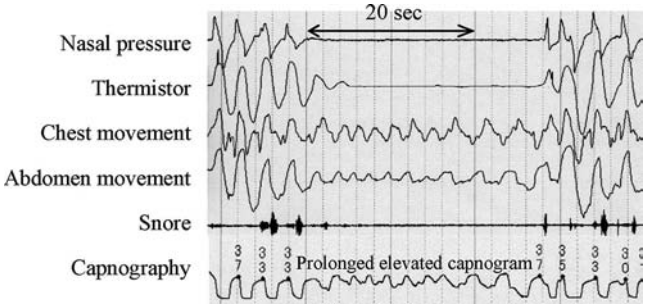
INTRODUCTION: Apnea detected by capnography is defined as no detection of CO_2 for 10, 20, or 30 s. However, capnography during sleep apnea sometimes shows abnormal capnograms. To better measure this, we developed a small mainstream capnometer (cap-ONE, Nihon Kohden Corp., Tokyo Japan) that fits under the nose of nonintubated patients. Previously, we reported that cap-ONE, which does not need aspiration of expired gas, can reliably measure capnography during both nasal and oral breathing (1,2). In this study, we examine capnograms obtained by cap-ONE during sleep apnea.

METHODS: The cap-ONE consisted of an infrared light unit, an infrared detector unit, and a nasal adaptor, which collects expired gas. The nasal and oral gases were expired directly into the cap-ONE through the nasal tube and mouth guide of the nasal adaptor, respectively, to measure capnography. We recorded both polysomnography (PSG) and capnography for five patients with sleep disorder and examined 193 apnea events that were detected with PSG.



PSG recording during obstructive apnea.

No CO_2 detection for more than 10 s	116 (60%)
Presence of prolonged elevated capnogram	049 (25%)
Presence of other irregular capnograms	028 (15%)

RESULTS AND DISCUSSION: The table lists the number of capnograms during apnea events in each category.

Expired CO_2 was shown in the capnograms of 40% of all apnea events in PSG. Small ripples were sometimes superimposed on the prolonged elevated capnogram during obstructive apnea (Fig. 1). The peaks of the ripples indicate that patients can exhale briefly and intermittently. Shallow valleys between the peaks indicate slight or no inhaling due to airway obstruction. The cap-ONE can measure this because expired gas remains in the cap-ONE until inhaling starts. Sidestream capnometers cannot measure this because they need continuous aspiration of expired gas and the remaining expired gas is easily diluted with the air. Sidestream capnometers may incorrectly show deep valleys in the capnogram as if the patient can inhale during the obstructive apnea. The cap-ONE sometimes detected expired CO_2 as irregular capnograms in shallow breathing that is difficult to detect with conventional nasal pressure transducers or thermistors.

CONCLUSION: In polysomnography, the cap-ONE can reveal much more precisely how each respiratory event happens in a patient with sleep apnea.

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A New Model of Pulse Oximetry: Two-Dimensional Pulsation

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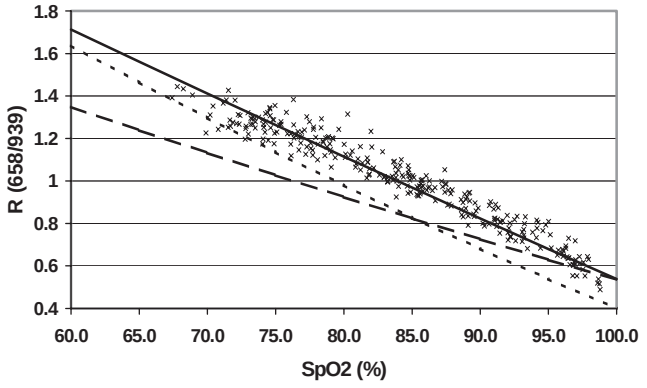
INTRODUCTION: We developed a two-dimensional pulsation model of pulse oximetry. Instead of a one-dimensional single layer as in the conventional theory, the arteries pulsate in two dimensions taking



into account the effect of probing light that does not pass through the arteries. Computer simulation results based on this model agree well with human test results.

MODEL: The arteries are modeled with a rectangular cross-section with horizontal width of W_a and vertical thickness (optical pathlength) l_a. Tissues outside of the artery are in an area lateral to the artery with width of W_T and the same thickness as the artery. Assuming the input optical power illuminates the artery and the tissue uniformly, the transmitted power, P, is composed of two parts, one that passes through the artery and one that does not. When the artery pulsates, the optical pathlength and the widths of the artery and the tissue change simultaneously. As a result, we derived the following equation for the relative change of transmitted optical power, equivalent to the change of optical density, dA, in the conventional theory.

$$dA = \frac{dP}{P} = -\frac{\exp(-g_T l_a) - \exp(-g_a l_a)(1 - g_a l_a)}{W_r \exp(-g_T l_a) + \exp(g_a l_a)} \frac{dl_a}{l_a}.$$

In the equation, $W_r = W_T / W_a$ is the ratio of the widths of the two areas, g_T is the extinction of tissues outside the artery, and g_a the extinction of the artery due to O_2Hb and RHb absorptions, the blood oxygen saturation s, and scattering of the blood. The ratio, R, of dA at two different wavelengths, where the relative pathlength change, dl_a/l_a, is cancelled, is a function of s, and this function defines the calibration curve, R-Spo$_2$. In R, we have two parameters, l_a and W_r, that are not present in the conventional model and that represent human variations.

RESULTS: Data sets (×) of R-Spo$_2$ of 13 human subjects were collected at wavelengths of 658 and 939 nm. Computer simulations of this two-dimensional pulsation model (solid line —) and the conventional one-dimensional pulsation model with (dashed line – – –) and without (dotted line —) scattering were done at the same wavelengths as shown in the figure. In the simulation, $l_a = 0.8$ cm and $W_r = 0.5$.

CONCLUSIONS: The two-dimensional pulsation model gives a specific form of effects of tissue outside the arteries in pulse oximetry. This model provides us the theoretical calibration curve that more closely matches the empirical data than the conventional model and can extend to very low saturation.

