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# 10

## Invasive and Noninvasive Blood Gas Monitoring

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### 10.1 INTRODUCTION

Accurate assessment of blood gases is fundamental to supportive care in critical care medicine. Traditionally, blood gases have been measured by invasive sampling, either through an indwelling arterial catheter or by arterial puncture, and analyzed in the laboratory by blood gas analyzers. This presents significant drawbacks, mainly because of the prolonged delay between sample acquisition and the availability of the laboratory results. In neonatal applications, for example, frequent blood sampling can cause significant blood loss, especially for very small infants, unless microblood samples are used for analysis. Furthermore, blood gas values are available only intermittently and therefore indicate the status of the patient only at the time the blood sample was drawn. The inevitable delay and lack of continuous information can lead to potential diagnostic errors, particularly in critically ill patients, in whom rapid and often life-threatening cardiopulmonary changes can occur during short periods of time. Continuous monitoring of blood gases, on the other hand, offers a major advantage since instantaneous changes in blood gas levels can be recognized and adequately corrected before irreversible tissue damage occurs. Furthermore, it provides trending information to assist in assessing the therapeutic response and predicting prognosis.

Recent advances in biosensors and medical instrumentation have made continuous blood gas monitoring a widely accepted diagnostic practice. There are three major groups of patients in whom blood gas monitoring is especially essential: patients suffering from acute respiratory or cardiovascular failure, premature neonates, and patients undergoing cardiac surgery. The most important clinical applications of blood gas monitoring include (1) assessment of acid-base disorders; (2) detection and management of hyperoxia, hypoxia, and hypercapnia, and (3) detection of right-to-left shunts and dead space ventilation.

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In this chapter we present the basic methods that have been developed for continuous blood gas monitoring. It is intended not to provide an exhaustive coverage of the topic, but rather to give the reader a fundamental knowledge of this emerging new field. In this chapter we review the principles of invasive and noninvasive monitoring of mixed venous oxygen saturation ( $SvO_2$ ), arterial oxygen saturation ( $SaO_2$ ), oxygen tension ( $pO_2$ ), pH, and carbon dioxide tension ( $pCO_2$ ) utilizing electrochemistry, spectrophotometry, gas chromatography, and mass spectrometry techniques.

## 10.2 BLOOD GAS TRANSPORT

### 10.2.1 $O_2$ Transport

Oxygen is transported by the blood from the lungs to the tissues in two distinct states. Under normal physiological conditions, approximately 2% of the total amount of  $O_2$  carried by the blood is dissolved in the plasma. The remaining 98% is carried inside the red blood cells in a loose reversible combination with hemoglobin (Hb), as oxyhemoglobin ( $HbO_2$ ). The amount of  $O_2$  in the blood depends on its  $pO_2$ . The amount of dissolved  $O_2$  is linearly proportional to the blood  $pO_2$ . The amount of  $O_2$  chemically combined with Hb, on the other hand, is related to the  $pO_2$  nonlinearly and is described by the sigmoid-shaped oxyhemoglobin dissociation curve (ODC). Accordingly, as the  $pO_2$  increases, there is a progressive but nonlinear increase in the blood oxygen saturation (i.e., the ratio between the  $O_2$  content to the maximum  $O_2$  carrying capacity expressed as a percentage). This nonlinear relationship ensures efficient transport of  $O_2$  to the tissues by the blood. Using this curve, and assuming a healthy patient, an approximate oxygen saturation value can be calculated from the  $pO_2$  measured in the laboratory by in vitro blood gas analysis, or vice versa. However, large errors may result in unhealthy patients or under abnormal physiological conditions. This is due mainly to variations in the blood pH, body temperature, the elevated level of 2,3-diphosphoglycerate (DPG),  $pCO_2$ , and type of functional Hb (e.g., adult HbA or fetal HbF). These factors play an important role in controlling the affinity with which Hb binds and releases  $O_2$ , and thus can cause a shift in the ODC. Therefore, to avoid errors inherent in this relationship, it is preferred to measure oxygen saturation directly rather than to measure  $pO_2$  and then estimate oxygen saturation from the ODC if the factors causing the shift in the curve are not taken into account. Normally, arterial blood has a  $pO_2$  of about 100 mm Hg (13.3 kPa), which corresponds to an oxygen saturation of approximately 98%. The  $pO_2$  of venous blood is normally about 40 mm Hg (5.3 kPa), which corresponds to an oxygen saturation of approximately 75%.

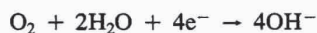
### 10.2.2 $CO_2$ Transport

$CO_2$  is carried by the blood both in a dissolved state and in combination with Hb and plasma proteins as carbamino compounds. The dissolved  $CO_2$  in the blood reacts with water to form carbonic acid, which is subsequently dissociated into hydrogen and bicarbonate ions. The reversible combination of  $CO_2$  with water accounts for approximately 70% of the total  $CO_2$  transported by the blood under normal resting conditions. The remaining  $CO_2$  is transported in the dissolved state (approximately 7%) and in a loose reversible combination with Hb as carbaminohemoglobin (approximately 23%). The total amount of  $CO_2$  carried by the blood is a function of the blood  $pCO_2$ . It is important to note that this relationship is a function of the blood  $pO_2$ , since binding of  $O_2$  with Hb tends to displace  $CO_2$  from the blood. The normal  $pCO_2$  of arterial blood is about 40 mm Hg (5.3 kPa), whereas that of venous blood is about 45 mm Hg (6 kPa).

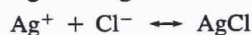
### 10.3 ELECTROCHEMISTRY OF $pO_2$ AND $pCO_2$ MEASUREMENT

#### 10.3.1 $pO_2$ Measurement

Measurement of  $pO_2$  is based on the principle of polarography as shown schematically in Fig. 10.1. Accordingly,  $O_2$  molecules dissolved in an electrolyte (e.g., KCl) are reduced at the surface of a noble metal cathode (e.g., platinum or gold). A constant polarizing voltage of approximately -600 mV is applied between the cathode and an adjacent reference Ag/AgCl anode. This polarizing voltage is required to minimize the interference of other gases that can also be reduced and to assure rapid oxygen reduction at the cathode. The electrochemical reduction at the cathode can be described by the following chemical reaction:



According to this reaction, an  $O_2$  molecule takes four electrons from the cathode, then reacts with two water molecules, generating four hydroxyl ions. The hydroxyl ions created in this reaction are buffered by the electrolyte. At the Ag/AgCl reference anode, the chemical reaction is



Silver from the electrode is first oxidized to silver ions and electrons are liberated to the anode. The silver ions immediately combine with chloride ions to form silver chloride which precipitates on the electrode surface. Consequently, there is a continuous flow of electrons (current) between the cathode and the anode, the rate of which is linearly proportional to the supply of  $O_2$  to the cathode. Since all  $O_2$  molecules reaching the cathode will react with it, the  $pO_2$  at the cathode surface is zero. In practice, the current generated is linearly proportional to the  $pO_2$  in the electrolyte. Thus, by measuring the change in current between the cathode and the anode, one can determine the amount of oxygen dissolved in the electrolyte. For medical applications, bare electrodes are seldom used. Instead, the sensor is separated from the blood by a semipermeable membrane that permits

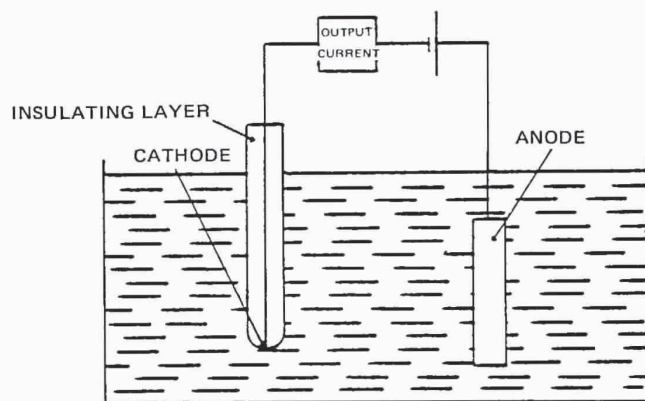


Fig. 10.1 Principle of polarographic  $pO_2$  measurement.

either O<sub>2</sub>, CO<sub>2</sub>, or hydrogen ions to diffuse slowly into the polarographic electrode. This significantly decreases the instability of the electrode due to flow-dependent effects.

### 10.3.2 pCO<sub>2</sub> Measurement

The pCO<sub>2</sub> electrode operates according to the Stow-Severinghaus principle, in which a CO<sub>2</sub> change is sensed by a pH electrode.<sup>1,2</sup> The principle of pCO<sub>2</sub> measurement is illustrated schematically in Fig. 10.2. In practice, the CO<sub>2</sub> molecules diffuse into a bicarbonate solution through a semipermeable membrane. Subsequently, hydrogen and bicarbonate ions are formed according to the following chemical reaction:



As a result of this chemical reaction, a potential is generated between the glass pH and the reference electrode (e.g., Ag/AgCl). This potential can be calibrated knowing the CO<sub>2</sub> concentration in the solution. By means of the Henderson-Haselbach relationship, it can be shown that the measured pH is proportional to the negative logarithm of the pCO<sub>2</sub>.

### 10.4 PRINCIPLE OF OPTICAL OXIMETRY

The basis of oxygen saturation measurement relies on the difference in optical absorption spectra of Hb and HbO<sub>2</sub>, as illustrated in Fig. 10.3. Consequently, various optical methods for measuring oxygen saturation have been developed based on measuring the light transmission through, or reflection from, blood at two wavelengths: λ<sub>1</sub>, where a large difference in light absorption between Hb and HbO<sub>2</sub> exist (e.g., 660 nm), and λ<sub>2</sub>, an isobestic wavelength, where the absorption of light is independent of blood oxygenation (e.g., 805 nm). The absorption of light by a Hb solution (i.e., hemolyzed blood) can be accurately determined using Beer-Lambert's law, which can be written as

$$P_t = P_0 \times 10^{-\alpha cd} \quad (1)$$

where P<sub>t</sub> is the transmitted light power, P<sub>0</sub> the incident light power, α the specific

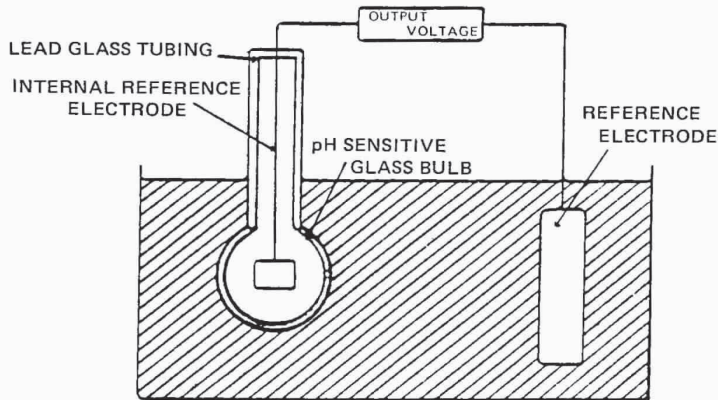


Fig. 10.2 Principle of electrochemical pCO<sub>2</sub> measurement.

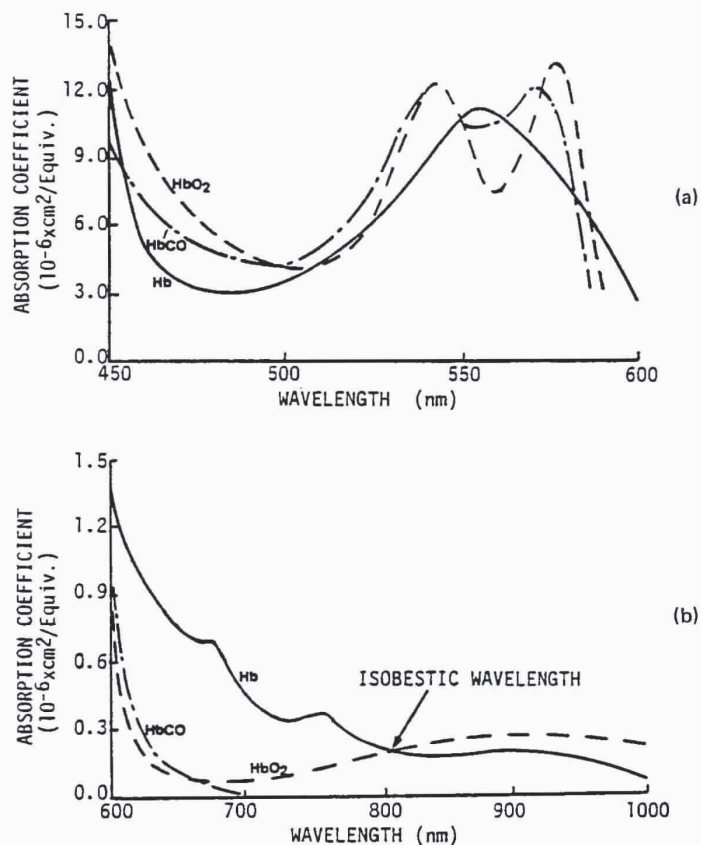


Fig. 10.3 Optical absorption spectra of Hb, HbO<sub>2</sub>, and HbCO.

absorption coefficient of the sample,  $c$  the concentration of the sample, and  $d$  the light-path distance.

Assuming that a hemolyzed blood solution consists of a two-component mixture (e.g., Hb and HbO<sub>2</sub>) and that light absorption by a homogeneous mixture of these two components is additive, the following relationship can be derived:

$$\text{oxygen saturation} = A - B \frac{\text{OD}(\lambda_1)}{\text{OD}(\lambda_2)} \quad (2)$$

where  $A$  and  $B$  are functions of the specific absorption coefficients of Hb and HbO<sub>2</sub>, and  $\text{OD}$  is the optical density [i.e.,  $\log_{10}(P_0/P_1)$ ] of the sample. It is important to keep in mind that this relationship is derived based on the assumption that hemolyzed blood obeys Beer-Lambert's law, which requires a monochromatic light source and collimated light

transmission through the sample. Furthermore, the solution cannot contain any particles that cause light scattering.

## 10.5 INVASIVE INTRAVASCULAR BLOOD GAS MONITORING

Efforts have been ongoing over the last decade to develop blood gas sensors which can be sufficiently miniaturized to enable intravascular placement. Several approaches have been developed utilizing electrochemical sensors, optical sensors, and indwelling sampling catheters connected to an external gas chromatograph or mass spectrometer.

### 10.5.1 Electrochemical Methods

#### pO<sub>2</sub> Sensors

Direct intravascular monitoring of pO<sub>2</sub> can be performed by a miniaturized bipolar polarographic sensor placed at the tip of a catheter.<sup>3-8</sup> Figure 10.4 illustrates a pO<sub>2</sub> sensor that consists of thin silver cathode and anode wires embedded in a 0.65-mm-diameter polyethylene tubing that acts as a gas-permeable membrane.<sup>5</sup> The Teflon insulation of the cathode wire is removed from the wire end over a length of 5 mm. The oxygen molecules diffuse through the walls of the polyethylene tube into an electrolyte gel and then reduced in an electrochemical reaction. The advantage of this particular catheter-tip configuration is that the measurement is performed on the sides of the probe and not at its tip, which has been shown to be particularly sensitive to fibrin deposits.

The sensor described above can be introduced into a femoral, brachial, or radial artery through a 4F (1.33-mm-diameter) plastic catheter. The tip of the sensor is then pushed forward so that it protrudes approximately 5 to 10 cm beyond the tip of the catheter. A special adapter can be used to monitor blood pressure and withdraw blood samples. The sensor is calibrated in situ by withdrawing and analyzing the pO<sub>2</sub> of a blood sample using a standard blood gas analyzer and adjusting the instrument reading accordingly.

A different type of polarographic sensor was described by Kimmich et al.<sup>6</sup> using solid-state fabrication techniques. The advantages of semiconductor integrated-circuit technologies were utilized because they allow one to design different miniature cathode and anode structures with good reproducibility and reasonable low cost. This particular pO<sub>2</sub> sensor was constructed in the shape of two rectangular spirals. The gold cathode and silver anode were deposited on a silicone substrate by vapor deposition. A porous

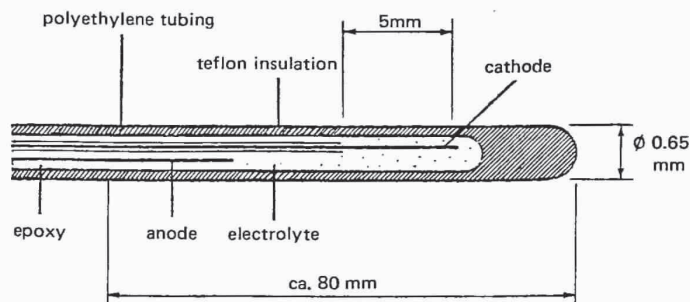


**Fig. 10.4** Cross section of an intravascular pO<sub>2</sub> catheter sensor.

cross-linked polymer matrix was used between the cathode and anode. A rubber membrane was utilized as a carrier for the electrolyte. The chip was then incorporated into a 4F (1.33-mm-diameter) catheter for intravascular measurements.

Neuman et al.<sup>9</sup> described a multicathode polarographic oxygen sensor which can be fabricated using either thick- or thin-film metallization techniques. This approach can be used to deposit defined structures of gold and silver films on an alumina substrate. In this particular sensor, a silicone dioxide film was used to delineate the exposed surface of the multiple gold cathode sites and the silver anode.

#### pCO<sub>2</sub> Sensors

A catheter-tip sensor for simultaneous monitoring of blood pCO<sub>2</sub> and pH has been developed by Coon et al.<sup>10</sup> This sensor consists of a palladium oxide (PdO) hydrogen-ion-sensitive electrode and an Ag/AgCl reference electrode. The electrodes are surrounded by a thin layer of bicarbonate solution and enclosed with a silicone polycarbonate pH-sensitive copolymer membrane. The entire catheter size is approximately 0.6 mm in diameter.

Blood pCO<sub>2</sub> is measured according to the Severinghaus-Stow technique with the PdO electrode being used to detect changes in the pH of the bicarbonate solution. An additional reference electrode outside the sensor but in direct contact with the blood is used for pH monitoring. The pH of the blood is a linear function of the measured potential generated between the Pd/PdO wire and the external reference electrode.

Kohama et al.<sup>11</sup> described a catheter-tip pCO<sub>2</sub> sensor based on a pH-ion-selective field-effect transistor (ISFET) technique. The sensor consists of a pH-sensitive ISFET and a Ag/AgCl reference electrode covered with a polyvinyl alcohol solution containing sodium bicarbonate and sodium chloride. The sensor is mounted inside a 0.73-mm-diameter silicone tube sealed with silicone resin.

### 10.5.2 Optical Methods

The development of fiber optic blood gas sensors has taken on special significance in recent years due to the availability of a variety of high-quality optical fibers, light sources, and detectors and is currently a very active area of research. The major challenge, however, is to make the catheter small enough to fit into blood vessels without obstructing the blood flow. Fiber optic sensors offer several advantages over traditional electrochemical electrodes. Some of these advantages include: immunity to electrical and electromagnetic interference, low drift (which is essential for long-term monitoring), and small size. The major challenges in developing a fiber optic blood gas sensor for medical application have been in the immobilization of the reagents used on the fiber tip, and making these sensors both biocompatible and sterilizable. Intravascular optical blood gas sensors fall into two categories: those that sense changes in the optical absorption of the blood directly (i.e., SvO<sub>2</sub> sensors) and those that use a reagent that changes its optical properties in response to changes in the analyte and the optical measurement is performed indirectly (i.e., pO<sub>2</sub>, pH, and pCO<sub>2</sub> sensors).

The basic construction of a fiber optic blood gas sensing system is shown schematically in Fig. 10.5. Light from a suitable source (LED, laser diode, or a combination of incandescent light and an interference optical filter) travels along an optical fiber by total internal reflection at the interface between a core and a cladding material having different refractive indices to a sensor at its tip. There the light interacts with the sample either

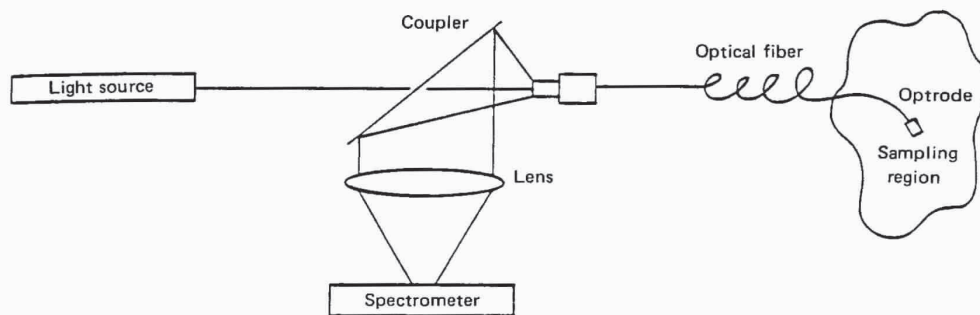


**Fig. 10.5** Principle of fiber optic blood gas sensing.

directly or indirectly through a specific reagent. The collected light then returns to a photodetector along either the same or a separate optical fiber, where it is processed.

Indirect fiber optic blood gas sensors use an immobilized reagent indicator that reacts with a specific analyte. An optical signal is produced in response to changes in the analyte concentration. The chemical reaction between the blood and the reagent can be reversible (the reagent used is not consumed) or irreversible (the reagent is eventually consumed). The measurement is performed by illuminating the sample with light at a known wavelength and intensity. Multiple wavelengths can also be used to measure several analytes simultaneously if the specific optical reaction results in sufficiently distinct absorption spectra.

Depending on the specific reaction monitored, either the attenuation of the incident light intensity due to absorption, reflection outside the fiber, or reflection along the surface of an uncladded fiber (attenuated total reflection or evanescent wave absorption) or the optical fluorescence produced (both emission and quenching) can be utilized to monitor the unknown sample concentration. Fluorescence-based sensors have many inherent advantages over the other optical sensing techniques. This advantage results from the fact that absorption measurements produce very small light attenuation that must be measured against a strong background light intensity. In fluorescence, on the other hand, the dye emits light at a wavelength different from that at which the excitation energy is absorbed. This too results in a small amount of light detected, but the measurement is made against a dark background that produces a much more sensitive and selective signal. Furthermore, a single fiber optic can be used to carry the excitation energy to the sample and return the fluorescence signal to the detector for analysis.

#### pO<sub>2</sub> Sensors

Oxygen quenching of luminescence occurs due to the transfer of energy from an excited molecule to molecular oxygen. The greater the collision frequency of oxygen molecules with excited molecules, the fewer excited molecules remain for optical detection. Therefore, the luminescence intensity decreases with increasing pO<sub>2</sub>. Utilizing this concept, Lubbers and Opitz<sup>12</sup> developed a fluorescence pO<sub>2</sub> sensor based on the O<sub>2</sub> quenching of pyrene butyric acid. A similar approach was devised by Peterson et al.<sup>13</sup> using the dye perylene dibutyrate. The dye was absorbed on polystyrene and contained in a porous polypropylene envelope. The pO<sub>2</sub> of the blood is measured by illuminating the dye with blue light and

detecting the yellow-green fluorescence intensity emitted. The ratio of the returned yellow-green to blue light intensity is processed according to the Stern-Volmer relationship, providing a readout proportional to  $pO_2$  according to

$$\frac{I_0}{I} = 1 + K(pO_2) \quad (3)$$

where  $I$  is the relative fluorescence intensity,  $I_0$  the intensity without  $O_2$  quenching, and  $K$  a calibration constant.

#### pH Sensors

Since most  $pCO_2$  measurements involve the measurement of pH, a brief discussion of relevant intravascular pH sensors is provided below. The first fiber optic blood pH sensor was developed by Peterson et al.<sup>14</sup> The basic design of this sensor is shown in Fig. 10.6. The sensing is performed in a miniature spectrophotometric cell made from an ion-permeable cellulose hollow fiber attached to the tip of two optical fibers. The special cell contains a pH-sensitive dye (phenol red) which is covalently bound to polyacrylamide microspheres. The dye is reversible and has two tautomeric forms, each with a different light absorption spectra. The relative proportions of the base form (absorbing green light) and the acid form (absorbing blue light) vary with pH. Green (560 nm) and red (600 nm) light is passed into the cell from one optical fiber. The green light is partially absorbed by the dye, while the red light that is not absorbed acts as a reference beam. A separate optical fiber collects the emitted light and passes it to a photodetector for processing. The ratio  $r$  of the green to red light intensities detected by the photodetector is related to the sample pH according to the equation

$$r = k \times 10^{-c/(10^{-d}+1)} \quad (4)$$

where  $k$  is a constant of the system,  $c$  the optical density at 560 nm when the dye is in its

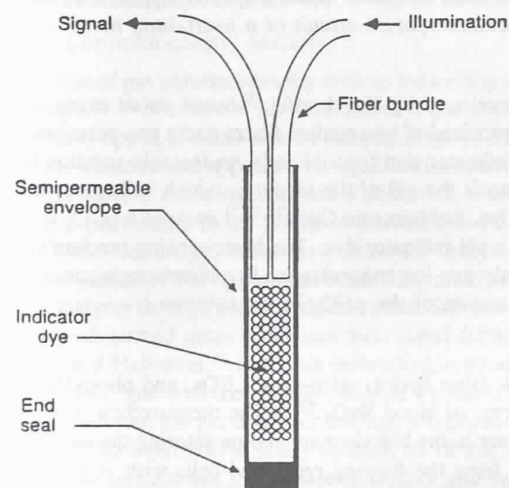


Fig. 10.6 Fiber optic pH sensor.

base form, and  $d$  the difference between the pH and pK of the dye. The sensor has been shown to be sensitive to pH in the range between 7.0 and 7.4 units with a precision of approximately  $\pm 0.01$  pH units.

Saari et al.<sup>15</sup> described a pH sensor using an immobilized fluoresceinamine dye bound covalently to cellulose. The pH is measured by exciting the dye at 480 nm and detecting the fluorescence emission produced at 520 nm. Jordon et al.<sup>16</sup> developed a different type of fiber optic pH sensor based on the work of Hirschfeld et al.<sup>17</sup> This approach is based on an absorption-emission technique in which a colorimetric reagent turns a fluorescent indicator dye on and off by radiationless resonance energy transfer (quantum tunneling). This technique combines the general availability of colorimetric reagents with the convenient features of fluorescent measurements. The sensor was constructed by immobilizing eosin (a fluorescent dye) and phenol red dyes in a polymer film at the end of an optical fiber. The fluorescence of the eosin was excited at 488 nm, a region of the spectrum where phenol red does not absorb light. Overlap of the eosin emission spectrum with the absorption spectrum of phenol red produces efficient energy transfer from the eosin, which is used as a donor molecule, to the phenol red, which is used as the acceptor molecule, resulting in a decrease of the eosin emission. As the pH is decreased, the phenol red absorbance shifts to shorter wavelengths, resulting in less efficient energy transfer and an increased eosin emission.

Recently, Gehrich et al.<sup>18</sup> developed a fiber optic pH sensor using a hydroxypyrene trisulfonic acid dye bonded covalently to a cellulose matrix which is attached to the fiber tip. Blood pH is calculated from the ratio of fluorescence intensity emitted at 520 nm measured with 460 nm excitation to that measured with 410 nm excitation light. This sensor is incorporated in one fiber optic catheter together with other proprietary  $pO_2$  and  $pCO_2$  sensitive dyes to measure simultaneously all three blood gas parameters. A similar optical fluorescence technique has been used also to develop an extracorporeal sensor for blood gases (Gas-STAT, Cardiovascular Devices, Inc., Irvine, California). This particular sensor was designed to monitor  $pO_2$ , pH, and  $pCO_2$  simultaneously in arterial and venous blood during open heart surgery. The sensor consists of proprietary fluorescence dyes and membranes for gases and hydrogen ions mounted inside a special disposable flow-through cell which is attached to the extracorporeal circuit of a heart-lung machine.

#### $pCO_2$ Sensors

A fiber optic  $pCO_2$  sensor has been developed by Vurek et al.<sup>19</sup> based on an extension of Peterson's work.<sup>14</sup> The sensor is comprised of two optical fibers and a gas-permeable silicone rubber tube filled with a pH indicator dye (phenol red), an isotonic solution of  $KHCO_3$ , and KCl. Ambient  $pCO_2$  controls the pH of the solution, which influences the optical transmission of the phenol red dye. Lubbers and Opitz<sup>12,20,21</sup> devised a  $pCO_2$  sensor utilizing  $\beta$ -methylumbelliferone as a pH indicator dye. The basic sensing mechanism is this dye, which detects changes in hydrogen ion concentration in a bicarbonate containing solution that in turn varies as a function of the  $pCO_2$  in the solution.

#### $SvO_2$ Sensors

The development of inexpensive plastic fiber optics, solid-state LEDs, and photodetectors has enabled direct in vivo monitoring of blood  $SvO_2$ .<sup>22-25</sup> The measurement is performed by placing a flexible fiber catheter in the bloodstream and monitoring the relative change in backscattered light intensity from the flowing red blood cells with variations in  $SvO_2$ . The optical fibers are incorporated into a disposable balloon-tipped catheter

catheter similar to a Swan-Ganz thermodilution catheter which is used for cardiac output measurement. The flow-directed catheter is typically inserted through the right heart into the pulmonary artery for monitoring mixed venous  $\text{SvO}_2$ . Central venous  $\text{SvO}_2$  monitoring is useful for detecting congenital heart defects that allow oxygenated blood to shunt into the venous side of the heart.

Figure 10.7 illustrates the principle of this measurement. The fiber optic catheter is connected to an optical module which contains the LEDs and photodetector. The incident light is transmitted to the blood through a source fiber. The backscattered light from the blood is collected by a second optical fiber located adjacent to the tip of the source fiber. Since  $\text{SvO}_2$  measurement is affected by blood flow and hematocrit, two wavelengths and the possibility of entering blood hematocrit by the user (TD catheter, American Edwards Laboratories, Santa Ana, California) or three wavelengths (Shaw Opticath, Oximetrix, Inc., Mountain View, California) are typically used to compensate for these effects. Further corrections for hematocrit variations can be achieved if two unequally spaced detecting fibers are incorporated in the catheter.<sup>26</sup> The light intensities emanating from the catheter tip are usually normalized by placing a standard reflecting surface over the catheter tip before the catheter is inserted into the blood. An empirically derived equation relating  $\text{SvO}_2$  to the infrared (IR)/red (R) reflectance ratio such as

$$\text{SvO}_2 = K_1 - K_2 \frac{\text{IR}}{\text{R}} \quad (5)$$

where  $K_1$  and  $K_2$  are constants depending on the catheter configuration and the optical properties of the blood, is typically used for processing the signals by the oximeter.

### 10.5.3 Gas Chromatography and Mass Spectrometry Methods

In addition to indwelling catheters where the measurement is performed intravascularly using a miniaturized electrochemical or optical sensor, it is also possible to remove a gas sample of the blood utilizing a carrier gas or a vacuum and feed the sample to an external gas chromatograph or mass spectrometer for analysis.

#### Gas Chromatography Sensors

The use of gas chromatography with an indwelling catheter has been investigated by several groups.<sup>27-31</sup> Massaro et al.<sup>29</sup> described a gas chromatograph blood gas sensor based on a closed-tipped 2F intra-arterial catheter (Fig. 10.8). The blood gases diffuse into the lumen of the catheter and approach an equilibrium concentration with the carrier gas contained in the lumen. After equilibrium is achieved, which takes approximately 4 min, a bolus of the gas content in the lumen is delivered to the gas chromatograph for separation and analysis. Helium gas is delivered from the analyzer through the outer annular supply line in the catheter. The helium gas containing the equilibrated blood gases is drawn back into the analyzer through the central return line. Silicone rubber tubing which is highly permeable to the dissolved gases facilitates their rapid diffusion into the catheter lumen. Carlon et al.<sup>30</sup> and Hall et al.<sup>31</sup> tested an indwelling arterial catheter for blood gases connected to a Sentorr gas analyzer (Ohio Medical Products, Madison, WI). The blood gases are aspirated into the gas analyzer through a heparin-coated helium-filled probe that was inserted into a peripheral artery through an 18-gauge catheter. Common problems with all of these sensors are inadequate reliability and safety.

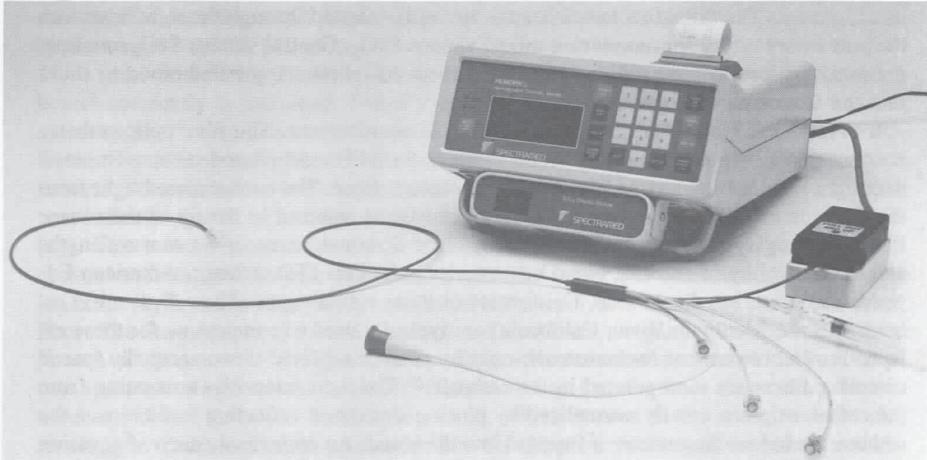


**Fig. 10.7** Fiber optic  $\text{SO}_2$  sensor and oximeter (courtesy of Spectramed, Oxnard, California).

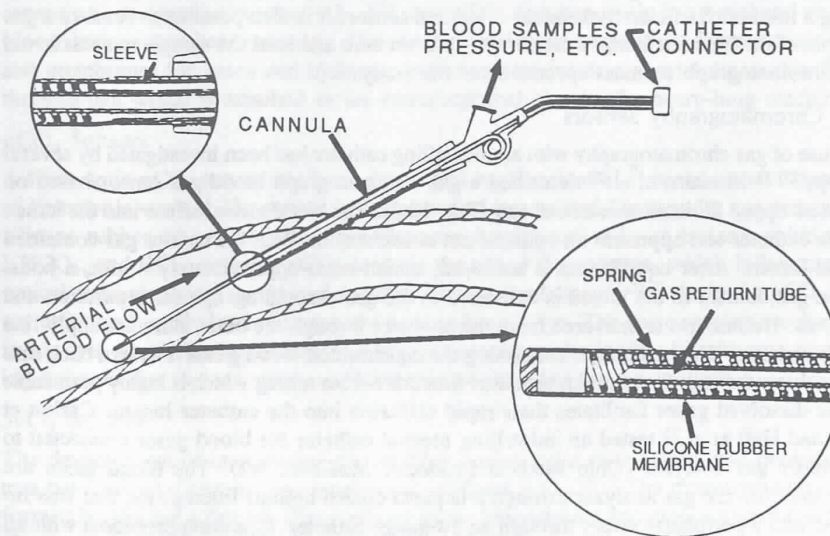


**Fig. 10.8** Gas chromatograph blood gas catheter.

### Mass Spectrometry Sensors

The continuous analysis of gases in blood with a mass spectrometer has been adapted for use with indwelling catheters.<sup>32,33</sup> Brantigan et al.<sup>34,35</sup> described the characteristics of different indwelling catheters for blood gas measurements using mass spectrometers. The catheters consist of a semipermeable polymer membrane mounted over a mandril of narrow-gauge flexible stainless steel tubing. In operation, the distal tip is placed in the blood and the proximal end is attached through 6 ft of connecting tubing to a vacuum inlet of the spectrometer. A pressure gradient is established which continuously draws a minute amount of gas across the membrane at a sampling rate of about  $2 \times 10^{-6}$  mL/s. The gases entering the mass spectrometer are analyzed according to their molecular weights.

## 10.6 NONINVASIVE BLOOD GAS MONITORING

Intravascular monitoring is not without limitations. Probe failure due to thrombotic deposition on the sensing element can be a serious problem and can provide a source of emboli and infection. Noninvasive monitoring (i.e., where there is no direct contact between the blood or other tissue fluids and the sensor) has, therefore, been the subject of extensive research and immense development for many years.

### 10.6.1 Gas Diffusion through the Skin

To understand the basics of O<sub>2</sub> and CO<sub>2</sub> diffusion through the skin, and some of the factors that affect noninvasive blood gas monitoring, it is important first to understand the physiology and anatomy of the human skin. The skin consists of three principal layers: the stratum corneum, epidermis, and dermis. The thickness of the human skin varies with age, sex, and region of the body. The outermost layer of the skin, the stratum corneum, is a nonliving layer composed mainly of dehydrated cells. Thus this dead layer does not consume any O<sub>2</sub> or produce CO<sub>2</sub>. The thickness of the stratum corneum varies from 0.1 to 0.2 mm, depending on the part of the body. Underneath the stratum corneum is the living, blood-free, epidermis layer. The epidermis consists of proteins, lipids, and melanin-forming cells which provide the skin with its characteristic brown color. The thickness of the epidermis can range from about 0.05 to 1 mm. The third layer of the skin is the dermis, which consists of dense connective tissue, hair follicles, sweat glands, fat cells, and a dense layer of capillaries. These capillaries are arranged in vertical loops approximately 0.2 to 0.4 mm long. The capillaries receive blood from arterioles, which are arranged in the form of a flat network parallel to the surface of the skin below the dermis. Arteriovenous anastomoses innervated by nerve fibers are commonly found in the dermis of the palms, face, and ears. These shunting blood vessels regulate blood flow through the skin. Blood flow through these channels can increase nearly 30-fold in response to heat.

Gas diffusion through the skin occurs due to a partial pressure between the blood in the dermis and the outermost surface of the skin. Diffusion of O<sub>2</sub> and CO<sub>2</sub> through the skin is normally very low. For example, it has been shown that under normal physiological conditions, the pO<sub>2</sub> measured on the surface of the skin is less than 2.5 mm Hg (0.33 kPa). However, when the skin is heated to approximately 43 °C, it becomes much more permeable to gases.

### 10.6.2 Electrochemical Methods

#### Transcutaneous pO<sub>2</sub> Sensors

In 1951, Baumberger and Goodfriend<sup>36</sup> reported that they had been able to determine arterial pO<sub>2</sub> successfully through the intact human skin. By immersing a finger in a phosphate buffer solution heated to 45 °C, they found that the pO<sub>2</sub> of the buffer approached that of the alveolar air. Soon thereafter, the physiologic observations of Evans and Naylor<sup>37</sup> and the development by Clark<sup>38</sup> of the membrane-covered polarographic pO<sub>2</sub> electrode led to the development by Lubbers,<sup>39</sup> Huch et al.,<sup>40</sup> and Eberhard et al.,<sup>41</sup> in the early 1970, of a skin sensor for transcutaneous pO<sub>2</sub> measurements.

The transcutaneous pO<sub>2</sub> electrode is operated in the “plateau” region of the polarogram, which is dependent on the rate of O<sub>2</sub> diffusion to the cathode and is independent of the applied polarization voltage. The process takes place behind a membrane that is permeable to O<sub>2</sub>, but separates the electrode from its surroundings. The thickness and composition of the membrane determines the rate of O<sub>2</sub> diffusion. For example, thicker membranes prolong the response time by significantly increasing the diffusion time. The most commonly used membrane materials in polarographic pO<sub>2</sub> electrodes include Teflon, polypropylene, and polyethylene. Since the O<sub>2</sub>-dependent current flow exhibits a linear relationship, only two known gas mixtures are required for calibrating a pO<sub>2</sub> electrode. Two in vitro calibration techniques can be employed: (1) using two precision gas mixtures (e.g., nitrogen and oxygen) and (2) using a “zero O<sub>2</sub> solution” (e.g., sodium sulfite) and ambient air. Once calibrated, sufficient stability is usually maintained. Typically, the drift of a transcutaneous pO<sub>2</sub> electrode is on the order of  $\pm 2$  mm Hg/h ( $\pm 0.3$  kPa/h).

Figure 10.9 illustrates a cross section of a typical Clark-type transcutaneous pO<sub>2</sub> sensor.<sup>42</sup> This sensor consists of three glass-sealed Pt cathodes that are separately connected via current amplifiers to a surrounded Ag/AgCl cylindrical anode ring. A buffered KCl electrolyte, which has a low water content to reduce drying of the sensor, is used. The two electrodes are covered with a thin layer of the electrolytic solution that is

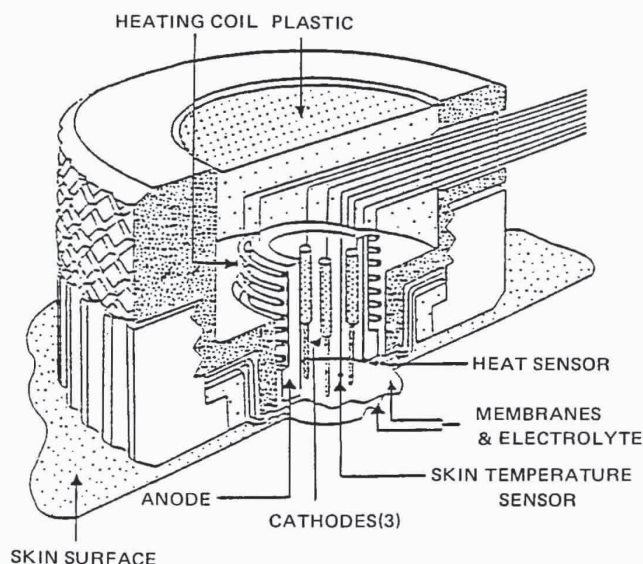


**Fig. 10.9** Cross-section diagram of a transcutaneous PO<sub>2</sub> sensor.

maintained in place by a membrane. This allows a slow diffusion of  $O_2$  from the skin into the sensor.

The diffusion of  $O_2$  through the skin is normally very low. Under normal physiological conditions, the  $pO_2$  measured at the surface of the skin using a nonheated transcutaneous  $pO_2$  electrode is nearly zero, regardless of the underlying blood  $pO_2$ . To facilitate  $O_2$  diffusion through the skin, abrasion of the skin and drug-induced hyperemia through the application of nicotinic acid cream were used initially. However, since direct skin heating gives a more prolonged and consistent effect, a heating element is now used in all commercial transcutaneous  $pO_2$  sensors. Generally, temperatures between  $43^\circ\text{C}$  in premature infants and  $44^\circ\text{C}$  in term infants yield adequate vasodilation of the cutaneous blood vessels with minimal skin damage. Heating the skin speeds up  $O_2$  diffusion through the stratum corneum. In addition, it causes vasodilation of the dermal capillaries, which increases blood flow to the region of skin in contact with the sensor. With increased blood flow, more  $O_2$  is available to the tissues surrounding the capillaries in the skin, and consequently, the  $pO_2$  of the blood in these capillary loops more closely approximates that of the arterial blood. Thus measurement by the transcutaneous sensor approaches more closely the  $pO_2$  of the arterial blood. Heating the blood also shifts the ODC to the right. Therefore, binding of Hb with  $O_2$  is reduced and the release of  $O_2$  to the cells is increased. Note also that simultaneously, heat also increases local tissue  $O_2$  consumption. Fortunately, however, these two factors tend to cancel each other.

Typical transcutaneous  $pO_2$  sensors have a round, snap-on plastic ring for mounting purposes. Attachment of the sensor to the skin is achieved using a double-sided, self-adhesive transparent tape. It is essential to ensure a gastight seal around the electrode; otherwise, ambient air will diffuse into the electrode. This will result in erroneous high  $pO_2$  readings. Approximately 10 to 15 min is normally required after mounting of the electrode before adequate skin vasodilation is achieved. Monitoring duration depends on the sensitivity of the skin to possible burns, as well as electrode drift. Usually, 4 to 6 h of continuous monitoring is possible before changing skin sites is recommended.

Some commercially available transcutaneous  $pO_2$  monitors measure and display the power required to heat the skin and maintain a constant sensor temperature. This power can be used to indicate "relative local tissue perfusion." For example, a decrease in the power level is indicative of a decrease in skin circulation, and vice versa. However, accurate determination of skin blood flow is not possible using this approach mainly because the heater power is susceptible to a great extent to surrounding ambient air and body temperature fluctuations.

During the past decade, transcutaneous  $pO_2$  monitoring has found numerous applications in both clinical medicine and physiological research. A wealth of information on the application of transcutaneous  $pO_2$  is available in several excellent monographs.<sup>43-45</sup> To date, the principal application has been in intensive care of newborns. This is due primarily to the relatively thin layer of the epidermis at birth and the frequent need to measure  $O_2$  in infants suffering from respiratory distress. The main rationale for monitoring  $pO_2$  in sick infants relates to the need for administering supplemental  $O_2$  while preventing dangerous high arterial  $pO_2$  that, in preterm infants, can lead to retinal and pulmonary tissue damage. Low  $pO_2$ , on the other hand, may cause death.

Under appropriate physiological conditions, good correlation between transcutaneous and arterial  $pO_2$  is normally obtained when the patient is not in shock or in hypothermia. During shock, it has been observed in dogs<sup>46</sup> and humans<sup>47</sup> that transcutaneous  $pO_2$  correlates well with cardiac output and therefore may be used to represent  $O_2$  delivery to tissue.

In hemodynamically unstable patients, transcutaneous  $pO_2$  does not usually equal arterial  $pO_2$ . Even with proper sensor heating, any significant decrease in skin perfusion that alters the flow of blood beneath the sensor, and thus the diffusion of  $O_2$  through the skin, will lead to low  $pO_2$  readings that may be as high as 50% of the true arterial  $pO_2$ . For example, in severe hypothermia, acidemia, anemia, or shock, skin perfusion may be compromised, and thus transcutaneous  $pO_2$  readings will no longer correlate with central arterial  $pO_2$ .

In adults, transcutaneous  $pO_2$  is usually 20 to 40% lower than arterial  $pO_2$  even at a sensor temperature of  $45^\circ\text{C}$ . This is attributed to the greater skin thickness, which requires intolerably high sensor temperatures to compensate for the greater effect of metabolism. Although transcutaneous  $pO_2$  monitoring is not widely used in the care of adult patients, studies have shown that it can be useful for evaluating the adequacy of cutaneous circulation in patients with peripheral vascular disease,<sup>48,49</sup> during shock and cardiopulmonary resuscitation,<sup>50,51</sup> and during exercise.<sup>52,53</sup>

#### Transcutaneous $pCO_2$ Sensors

Continuous  $pCO_2$  monitoring can be advantageous in monitoring lung dysfunction and preventing respiratory alkalosis and acidosis. For example, early respiratory failure is often recognized from an abnormal rise in arterial  $pCO_2$ . Furthermore, when artificial ventilation is required,  $pCO_2$  monitoring makes it easier to adjust the parameters of the respirator to suit the specific physiological needs of the patient.

A typical transcutaneous  $pCO_2$  sensor, which is similar in many respects to a transcutaneous  $pO_2$  sensor, is illustrated in Fig. 10.10. This sensor consists of a glass pH electrode with a concentric Ag/AgCl reference electrode that also serves as a temperature-controlled heater. A small amount of buffer electrolyte (e.g.,  $HCO_3^-$ ) is placed on the surface of the electrodes and a thin  $CO_2$  permeable membrane (e.g., Teflon) is stretched over the electrode to separate the sensor from its surroundings.

Since a  $pCO_2$  sensor has a high temperature coefficient, it must be calibrated at a temperature at which it will be operated. The effects of heating a transcutaneous  $pCO_2$  sensor must therefore be considered when interpreting the measurements. Heating the sensor results in an increase in (1)  $pCO_2$ , since the solubility of  $CO_2$  gas decreases; (2) local tissue metabolism; and (3) the rate of  $CO_2$  diffusion through the stratum corneum layer.

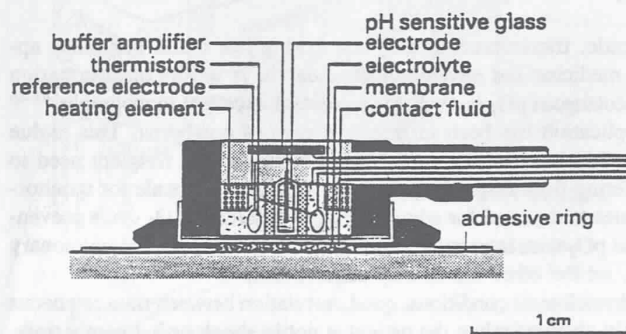


Fig. 10.10 Cross-section diagram of a transcutaneous  $PCO_2$  sensor.

Therefore, transcutaneous  $p\text{CO}_2$  values are higher than the corresponding arterial  $p\text{CO}_2$ . Despite this difference, the correlation between transcutaneous  $p\text{CO}_2$  and arterial  $p\text{CO}_2$  is usually satisfactory. Because the electrical signal obtained from a transcutaneous  $p\text{CO}_2$  sensor is proportional to the logarithm of the  $\text{CO}_2$  concentration, there is no "zero-point" calibration as in a transcutaneous  $p\text{O}_2$  sensor. Therefore, one needs two different precisely analyzed gas mixtures for calibration. Usually, gas mixtures containing 5 and 10%  $\text{CO}_2$  are used for calibrating a transcutaneous  $p\text{CO}_2$  sensor.

Since  $\text{CO}_2$  produced by epidermal cells diffuses to the dermal capillaries, transcutaneous  $p\text{CO}_2$  values are higher than the corresponding blood  $p\text{CO}_2$ . The counter-current blood gas exchange mechanism in the dermal capillaries causes  $\text{CO}_2$  diffusion between the parallel arterial and venous sides of the capillary bed. The rising arterial side picks up  $\text{CO}_2$  from the existing venous side. Therefore, venous  $p\text{CO}_2$  is lower than arterial blood and a maximum  $p\text{CO}_2$  gradient is established at the tips of the capillary loops. Because of this mechanism, skin surface  $p\text{CO}_2$  is higher than venous  $p\text{CO}_2$  even if the transcutaneous  $p\text{CO}_2$  sensor is not heated.

Generally, good correlations between arterial and transcutaneous  $p\text{CO}_2$  have been observed. Cassady<sup>54</sup> compared transcutaneous  $p\text{CO}_2$  with arterial  $p\text{CO}_2$  and found that published data consistently show intercept values different from zero. In addition, a wide variation in slope values were also noticed. Severinghaus<sup>55</sup> has noted that transcutaneous  $p\text{CO}_2$  values published in the literature have not generally been corrected, either for the temperature difference between the skin and the transcutaneous sensor or for skin metabolism. When these corrections are made, transcutaneous and arterial  $p\text{CO}_2$  values are in satisfactory agreement.

Tremper et al.<sup>56</sup> studied the relationship between transcutaneous  $p\text{CO}_2$ , arterial  $p\text{CO}_2$ , and cardiac output in dogs during hypercarbia and shock. By hemorrhaging dogs, it was observed that arterial  $p\text{CO}_2$  remained unchanged throughout the experiment. On the other hand, transcutaneous  $p\text{CO}_2$  increased when cardiac output decreased below 50% of the control. As blood volume was replaced, transcutaneous  $p\text{CO}_2$  returned to its original baseline. These findings demonstrated that in hypovolemic shock, transcutaneous  $p\text{CO}_2$  can be used as a good indicator of tissue  $\text{CO}_2$  levels.

Generally, it is accepted that transcutaneous  $p\text{CO}_2$  is a valuable trend monitor in neonates and adults who are not in shock. Since arterial  $p\text{CO}_2$  varies inversely with alveolar ventilation, transcutaneous  $p\text{CO}_2$  can provide immediate information concerning the effectiveness of spontaneous or mechanical ventilation. Tremper et al.<sup>57</sup> observed that in adult patients transcutaneous  $p\text{CO}_2$  values accurately follow the trend in arterial  $p\text{CO}_2$  when blood flow is normal. During severe low-flow shock conditions, when the cardiac index falls below 1.5 L/min per square meter, transcutaneous  $p\text{CO}_2$  rises relative to arterial  $p\text{CO}_2$  and the transcutaneous readings become primarily flow dependent.

### 10.6.3 Optical Methods

#### $p\text{CO}_2$ Sensors

Besides electrochemical techniques,  $\text{CO}_2$  diffusion through the skin has been measured using an infrared absorption technique. An example of such an application uses the Hewlett-Packard model 47210A capnometer and a special sensor.<sup>58</sup> This specially designed miniature sensor, which is normally used with the capnometer for airway measurement of  $p\text{CO}_2$ , has been adapted for transcutaneous  $p\text{CO}_2$  monitoring. The sensor consists of a light source, a filter wheel, and a detector mounted inside a small sealed chamber. The

absorption of light emitted from the infrared source is a function of the  $p\text{CO}_2$  inside the sealed chamber. The chamber is applied to a flat part of the skin, which must be previously prepared by removing the top dry layer of the skin with repeated applications of a specially designed adhesive tape. To enhance  $\text{CO}_2$  diffusion through the skin, the sensor is heated and maintained at a constant temperature of  $39^\circ\text{C}$ . This relatively low skin temperature minimizes the risk of skin burns and facilitates prolonged monitoring without the need for frequent site changes. Although satisfactory correlation between arterial and transcutaneously measured  $p\text{CO}_2$  has been demonstrated, this technique has had only limited clinical success mainly because of the inconvenience associated with preparing the skin prior to each measurement.

#### SaO<sub>2</sub> Sensors

*Ear Oximetry.* The first application of Beer-Lambert's law to noninvasive arterial SaO<sub>2</sub> measurement was suggested by Wood and Geraci in 1949.<sup>59</sup> Since the ear tissue is an imperfect optical cuvette and thus the light transmitted undergoes partial reflection and multiple scattering by both tissue and blood, initial attempts to measure arterial SaO<sub>2</sub> noninvasively required the subtraction of the light attenuated by the bloodless tissue from the total amount of light transmitted through the ear. This was accomplished by compressing the ear using a transparent pressure capsule that is initially inflated to a pressure that exceeds the arterial blood pressure (e.g., 200 mm Hg), thus rendering the ear pinna almost bloodless. After the light transmission through the bloodless ear is measured and a baseline is established, the pressure in the capsule is released and a second measurement is taken. Arterial SaO<sub>2</sub> was then determined from the difference in these two measurements. Although this approach was the first significant step toward an accurate noninvasive measurement of arterial SaO<sub>2</sub>, it was not very successful, due mainly to problems associated with the calibration of the ear probe, inadequate accuracy and reproducibility, and inconvenience.

The first widely used commercial ear oximeter was developed by Hewlett-Packard in 1970.<sup>60</sup> A photograph of the Hewlett-Packard model 47201A ear oximeter sensor is shown in Fig. 10.11, and the principle of its operation is shown in Fig. 10.12. A high-intensity tungsten lamp generates a broad spectrum of light. Eight narrow-band interference filters are mounted on a rotating wheel that intercepts the light path sequentially and provide a source of wavelength selection. These filtered light beam pulses enter a fiber optic cable that carries it to the ear. A second fiber optic cable carries the light pulses transmitted through the ear back to the instrument for detection and analysis. To measure arterial SaO<sub>2</sub>, the ear probe is attached to the pinna of the ear after the ear has been rubbed briskly for about 20 s to increase local blood flow. A temperature-controlled heater within the probe maintains a temperature of  $41^\circ\text{C}$ , causing an increase in local blood flow and proper blood "arterialization" after the ear probe has been properly positioned on the ear.

The Hewlett-Packard ear oximeter measures SaO<sub>2</sub> by comparing the intensity of the light passing through the ear at eight selective wavelengths between 650 and 1050 nm. It is assumed that the ear pinna acts as an optical cuvette and consists of a mixture of different light absorbers. The oximeter determines the light transmissions  $T_n$  of the ear by comparing the transmitted light intensity at each wavelength to the corresponding value stored during a brief standardization procedure before the ear probe is applied to the ear. The computation circuits derive SaO<sub>2</sub> according to Beer-Lambert's model of the ear using the equation

$$\% \text{ SaO}_2 = \frac{A_0 + \sum_{n=1}^8 A_n \log T_n}{B_0 + \sum_{n=1}^8 B_n \log T_n} \times 100 \quad (6)$$

where  $A_n$  and  $B_n$  are constants that were determined empirically on a diverse range of subjects breathing varying  $\text{O}_2$  concentrations.

The Hewlett-Packard ear oximeter measures arterial  $\text{SaO}_2$  continuously, accurately, and without involving the subject in any calibration or standardization procedures. The accuracy of the measurement is better than 2.6% saturation regardless of skin color and ear thickness. The response time of the oximeter can be selected by the operator and is changeable between 1.5 and 4.7s. Bilirubin concentration greater than 10 mg % will cause erroneously low readings. Furthermore, cardiogreen dye in concentrations used during cardiac output determination will cause transiently high  $\text{SaO}_2$  readings. The major disadvantage of the Hewlett-Packard ear oximeter is the weight of the fiber optic cable (approximately 100 g) and the size of the ear probe (approximately  $10 \times 10$  cm). This is a particular disadvantage in applications where monitoring of neonates and premature infants is desired. The Hewlett-Packard ear oximeter is no longer being manufactured.

**Pulse Oximetry.** A different optical approach to measure arterial  $\text{SaO}_2$  noninvasively has been suggested by Yoshiya et al.<sup>61</sup> The method is based on the assumption that the change in light transmitted through tissue during the inflow phase of the cardiac cycle (i.e., systole) is caused solely by the arterial blood. This is illustrated as a photoplethysmogram in Fig. 10.13. It is assumed that there is no pulse from the surrounding tissue and that the pulse of venous blood is normally insignificant. Consequently,

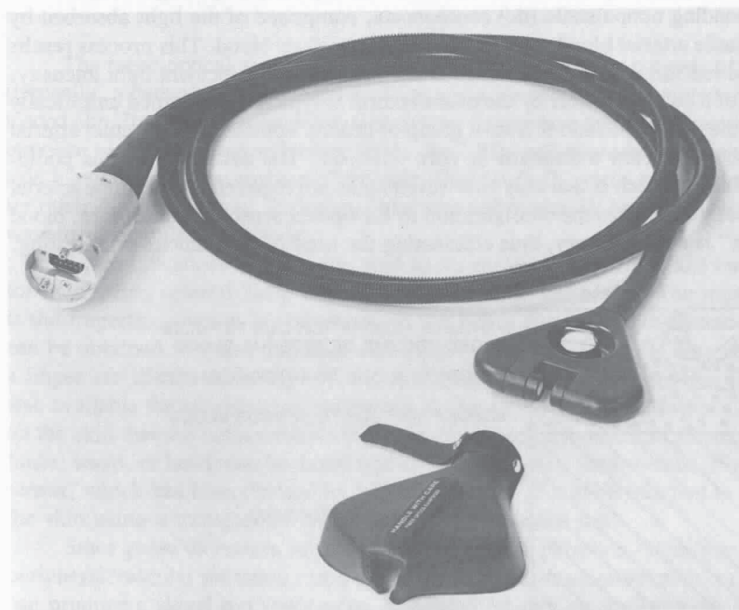


Fig. 10.11 Hewlett-Packard model 47201A ear oximeter sensor.

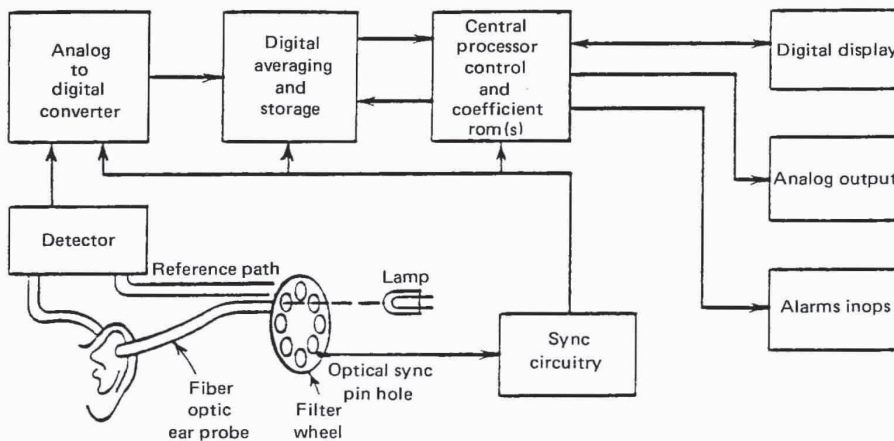


Fig. 10.12 Simplified diagram of the Hewlett-Packard model 47201A ear oximeter.

arterial  $\text{SaO}_2$  can be derived by analyzing only the changes in optical density caused by the pulsating arterial bed at a red wavelength (e.g., 660 nm) and a second (isobestic) infrared wavelength (e.g., 805 nm). Typically, a normalization process is performed by which the pulsatile (ac) component of the red and infrared photoplethysmograms is divided by the corresponding nonpulsatile (dc) components, comprised of the light absorbed by tissue, nonpulsatile arterial blood, venous blood, and capillary blood. This process results in a normalized red/infrared ratio  $R$ , which is independent of the incident light intensity. Precalibration of a pulse oximeter by the manufacturer is typically performed empirically by correlating the measured ratio  $R$  from a group of healthy volunteers with actual arterial  $\text{SaO}_2$  values obtained from a standard in vitro oximeter. The advantage of this photoplethysmographic approach is that only two wavelengths are required to determine arterial  $\text{SaO}_2$ . This greatly simplifies the configuration of the optical sensor. Furthermore, blood "arterialization" is not necessary, thus eliminating the need for continuous skin heating.

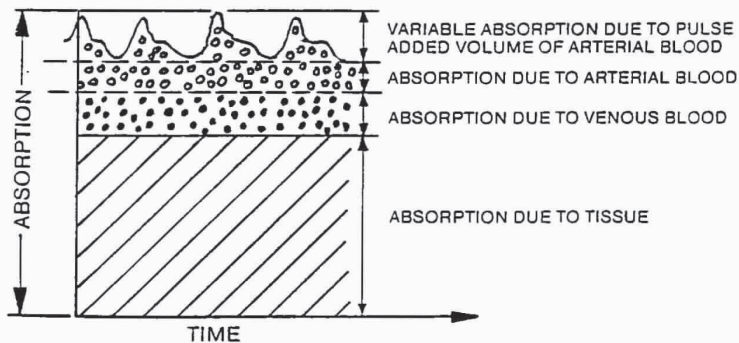


Fig. 10.13 Variations in light attenuation by tissue illustrating the rhythmic effect of arterial pulsation.

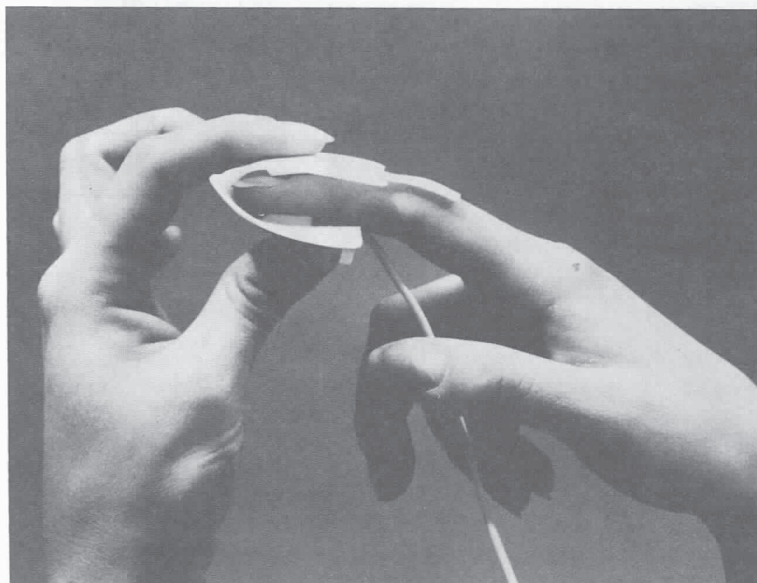


**Fig. 10.14** Finger probe assemblies of the Nellcor model N-100 pulse oximeter.

The basic optical sensor of a noninvasive pulse oximeter consists of a light source (typically, a pair of red and infrared LEDs) and a photodetector mounted inside a spring-loaded clip. In a transmission pulse oximeter the light source and photodetector are mounted opposite each other. In a reflection mode, the LEDs and photodetector are both mounted side by side facing the surface of the skin. Besides  $\text{SaO}_2$ , most pulse oximeters also offer other display features, including pulse rate and analog or bar graphs indicating pulse waveform or pulse amplitude.

Several locations on the body, such as the earlobes, fingertips, and toes, are suitable for monitoring arterial  $\text{SaO}_2$  with transmission pulse oximeters. The most popular site is the fingertip, since it is convenient to use and a good photoplethysmographic signal can be obtained. A pulse oximeter and finger sensor depicting the way it is attached to a finger are illustrated in Fig. 10.14. A slightly different configuration (Fig. 10.15) is also available for attaching a transmission sensor to the earlobe and foot. Other locations on the skin that are not accessible to conventional transillumination techniques (e.g., the limbs, torso, or head) can be monitored using a reflection  $\text{SaO}_2$  sensor (Fig. 10.16). The sensor, which has been devised by Mendelson et al.,<sup>62</sup> can be attached to the surface of the skin using a transparent, self-adhesive, double-sided tape.

Since pulse oximeters rely on adequate arterial pulsation, significant reduction in peripheral vascular pulsation, such as in hypotension, vasoconstriction, or hypothermia, can produce a signal too small to be processed reliably by the oximeter. Furthermore, motion artifacts can cause erroneous readings. Practically, these artifacts are reduced by digital processing of the analog signals and averaging the  $\text{SaO}_2$  values over several

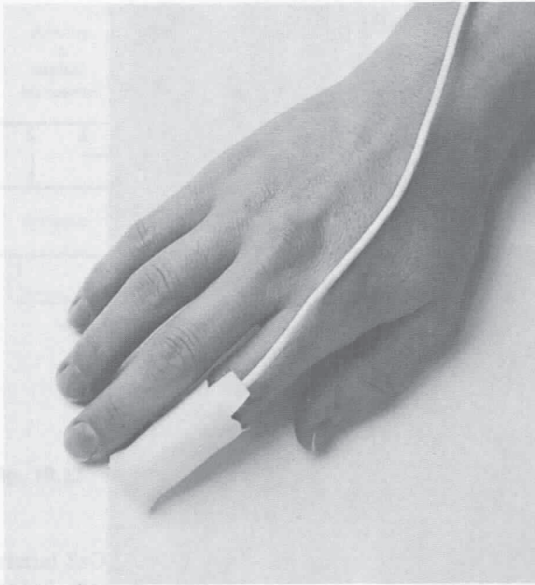


**Fig. 10.15** Finger probe of the Datascope pulse oximeter.

seconds before they are displayed. Nevertheless, despite these limitations, the fact that no calibration, stabilization time, or site preparation is required and the availability of a small, lightweight, and easy-to-apply noninvasive  $\text{SaO}_2$  sensor has made pulse oximetry a very useful and popular technique. Recently, the technique has been recommended as a standard of care for basic intraoperative monitoring.<sup>63</sup>

Noninvasive monitoring of  $\text{SaO}_2$  by pulse oximetry is becoming a rapidly growing practice in clinical medicine and physiological research. Pulse oximetry is widely used in various applications, including surgery, ICU, hypoxemia screening, exercise monitoring, controlling oxygen administration, sleep studies, and pulmonary function tests.<sup>64-67</sup> The availability of small, lightweight optical sensors makes  $\text{SaO}_2$  monitoring especially applicable for neonatal and ambulatory applications.

The use of pulse oximeters may be limited by interference from electrosurgical units and high-intensity light sources such as surgical lamps.<sup>68-70</sup> Furthermore, being a two-wavelength device, high concentrations of carbon monoxide, as in smoke inhalation victims, elevated bilirubin and methemoglobin levels, and intravenous dyes such as methylene blue, indigo carmine, and indocyanine green can cause inaccurate readings.<sup>71-75</sup> Considering the many possible sources of errors, the accuracy of noninvasive pulse oximeters is sufficient for many clinical applications. Most manufacturers claim that their instruments are accurate to within  $\pm 2\%$  (SD) in the  $\text{SaO}_2$  range between 70 and 100%.

#### 10.6.4 Gas Chromatography and Mass Spectrometry Methods

In addition to the optical and electrochemical techniques described above, other innovative methods for transcutaneous monitoring of blood gases, such as mass spectrometry<sup>76-80</sup>

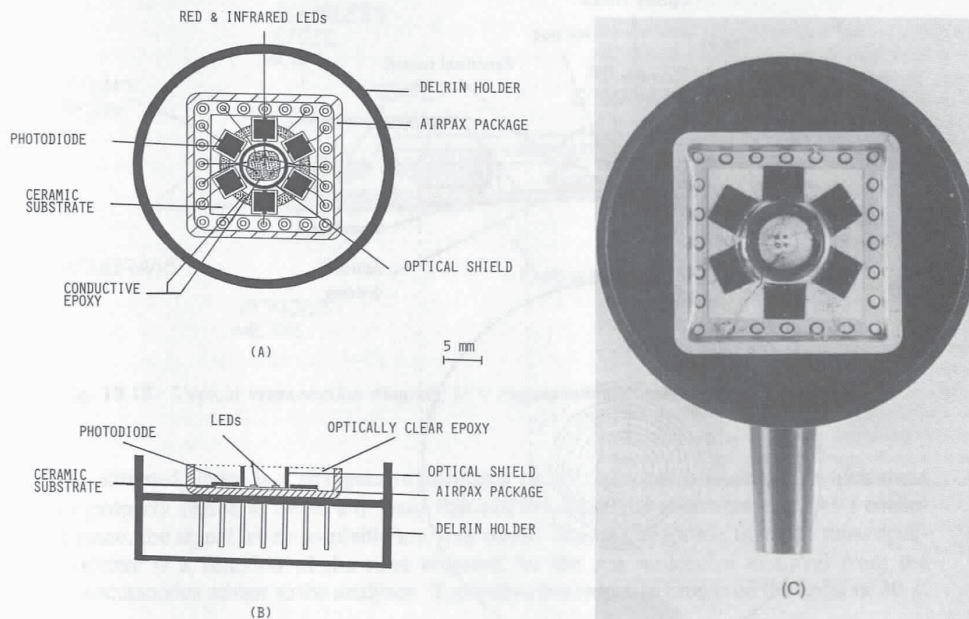


**Fig. 10.16** Noninvasive reflection  $\text{SaO}_2$  sensor.

and gas chromatography,<sup>81</sup> have been investigated. These techniques consist of a small, lightweight, and inexpensive skin sensor that is connected to a remote gas analyzer. Transcutaneously diffused gases are then collected in a heated chamber from which they are fed by a gas-impermeable line to a remote analyzer where several gases can be analyzed simultaneously.

#### Gas Chromatography Sensors

The gas chromatograph, like the mass spectrometer, is an instrument capable of separating and analyzing most of the gases of clinical interest using very small samples. Figure 10.17 illustrates a typical transcutaneous gas chromatograph sensor. The sensor consists of a metal body with a fine spiral groove machined across the center of the front face. The back contains a heating coil and a thermistor. The carrier gas (e.g., He or  $\text{N}_2$ ) enters the spiral groove and travels around it before it exits via the center. A small amount of sampled gas is injected into the carrier gas stream, which passes through a chromatograph column packed with small polymer beads. The various components of the sampled gas are separated according to the difference in the molecular forces exerted between the gas and the column material. Thus gases with higher affinities will tend to stay inside the column longer than will gases with relatively lower affinities. A thermal conductivity detector produces a series of short pulses corresponding to the different gas components present in the sample. These pulses are then integrated to provide the unknown amount of sampled gas. The primary disadvantage of transcutaneous gas chromatography is that

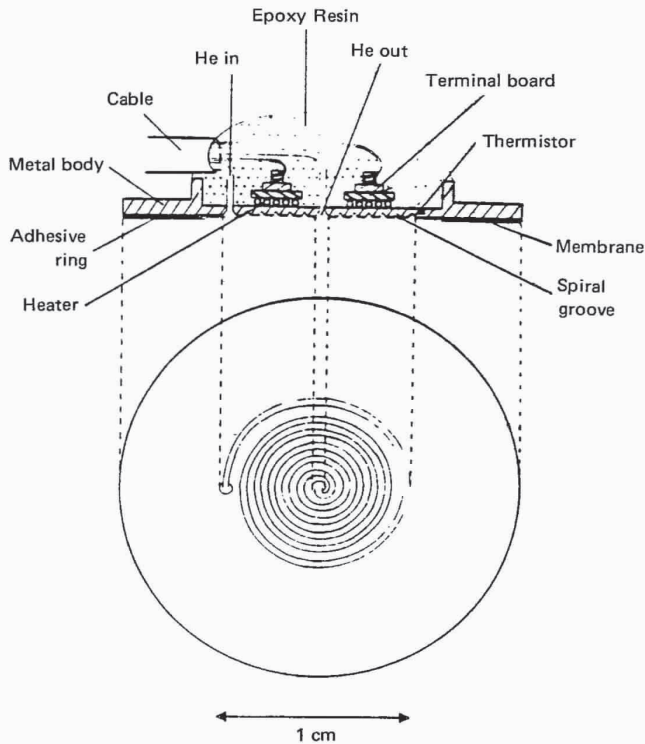


**Fig. 10.17** Typical cross-section diagram of a transcutaneous gas chromatograph sensor.

it is not possible to monitor gases on a continuous basis. This disadvantage may be outweighed by the fact that the system is less expensive and more portable compared to a mass spectrometer.

#### Mass Spectrometry Sensors

Transcutaneous mass spectrometry sensors have been utilized in limited clinical studies to demonstrate the feasibility of monitoring  $O_2$ ,  $CO_2$ ,  $N_2$ , and  $N_2O_2$  gases simultaneously. A schematic diagram of a typical transcutaneous mass spectrometer sensor is shown in Fig. 10.18. This sensor consists of a small stainless-steel chamber with a porous metallic substrate across its open face. Gases collected in this chamber pass by a vacuum pump along a gas-impermeable tube into the ion source of the mass spectrometer. The back of the sensor contains a heating coil and a thermistor for controlling the temperature of the sensor. A membrane is placed across the substrate and sealed to the skin with a double-sided, self-adhesive ring.

The major drawbacks of transcutaneous mass spectrometry and gas chromatography includes the possibility of gas leaks and the relatively slow response time. The amount of gas that can usually be removed from the skin without disturbing the tissue gas profile is limited to approximately  $10^{-7}$  mL/cm<sup>2</sup> per second. Since very low gas concentrations

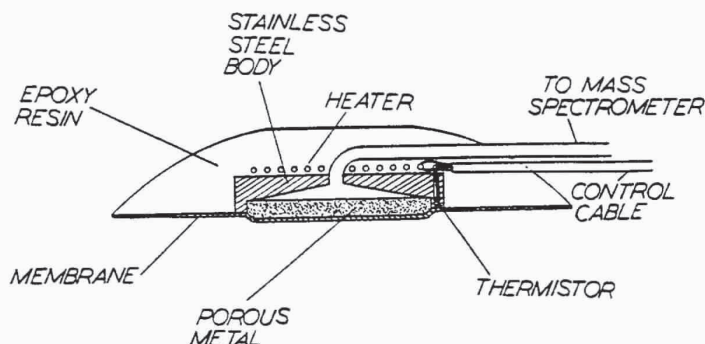


**Fig. 10.18** Typical cross-section diagram of a transcutaneous mass spectrometer sensor.

are obtained, there is a stringent requirement on the inlet gas connections, which must be properly sealed to avoid any leaks that can invalidate the measurements. As a consequence, the signal levels available are very small. The total response time of a mass spectrometer is a function of the time required for the gas molecules to travel from the transcutaneous sensor to the analyzer. Typically, this response time is on the order of 20 s.

#### 10.6.5 Cerebral Oxygenation Monitoring

Cytochrome  $aa_3$  (cytochrome  $c$  oxidase) is the terminal enzyme of the mitochondrial respiratory chain and catalyzes approximately 90% of all  $O_2$  utilization in the body. This enzyme is of particular importance in monitoring oxidative metabolism because it donates electrons directly to  $O_2$ . Therefore, the redox state of cytochrome  $aa_3$  is believed to be an indicator of intracellular  $O_2$  sufficiency. In the oxidized state this enzyme exhibits a distinctive absorption band in the 820 to 870 nm region of the spectra. This band disappears upon reduction when  $O_2$  delivery is compromised. Since Hb and  $HbO_2$  also absorb in this spectral region, multiple wavelengths and the application of appropriate algorithms are required to eliminate the interference of Hb and  $HbO_2$ .

Jobsis<sup>82</sup> described an optical method for noninvasive monitoring of cerebral  $O_2$  delivery and utilization. The technique involves monitoring the steady-state changes of the oxidation-reduction level of cytochrome  $aa_3$  in vivo together with changes in local blood volume and hemoglobin oxygenation. Three GaAlAs laser diodes with peak emission wavelengths between 760 and 904 nm were used as light sources. The light is guided to the subject's forehead by a glass fiber optic cable. The light backscattered from the brain, which is characteristic of changes in the optical absorption by cytochrome  $aa_3$  and Hb, is collected by a second fiber optic cable located approximately 5 cm lateral from the incident entry beam. The concept has been proven to be a feasible monitoring technique in animals<sup>83</sup> and humans.<sup>84</sup>

#### 10.6.6 Choroidal Eye Oximetry

A special eye oximeter for noninvasive measurement of choroidal blood oxygen saturation in the back of the eye has been developed by Laing et al.<sup>85</sup> and Delore et al.<sup>86</sup> The

measurement is made by shining a multiwavelength light beam into the eye and measuring the amount of light that is backscattered from the ocular fundus using a special fundus camera. Blood oxygen saturation is computed using conventional spectrophotometric oximetry techniques. Since the choroidal blood is characteristic of the blood supply to the brain, this approach has been suggested as a noninvasive diagnostic tool to monitor relative changes in oxygen saturation in the arterial blood supplying the brain.

#### 10.6.7 Palpebral Conjunctiva Monitoring

A palpebral conjunctival (i.e., inner eyelid) sensor, for measuring the  $pO_2$  in a vascular bed perfused by the ophthalmic artery has been developed by Kwan and Fatt<sup>87</sup> and Markle and Fink.<sup>88</sup> This eyelid sensor takes advantage of the unique function of the capillary bed in the palpebral conjunctiva, which is perfused by the internal carotid artery that supplies  $O_2$  to the avascular cornea during sleep. The conjunctival oxygen sensor is essentially a miniaturized unheated version of a Clark-type  $pO_2$  electrode mounted in an oval ophthalmic conformer ring as shown in Fig. 10.19. The conformer ring, which is made of a plastic biocompatible material (e.g., polymethyl methacrylate), is contoured to the shape of the sclera so that normal vision is not obstructed and free eye movement can be maintained. The device is designed to fit beneath the eyelid and is positioned such that the  $pO_2$  sensor abuts the inner surface of the superior eyelid. This maintains a close contact with the inner eyelid tissue. Wires emanating from the temporal side of the sensor are connected to the monitoring console. The primary limited applications of this  $pO_2$  sensor to date have been in emergency and critical care medicine.<sup>89-92</sup>

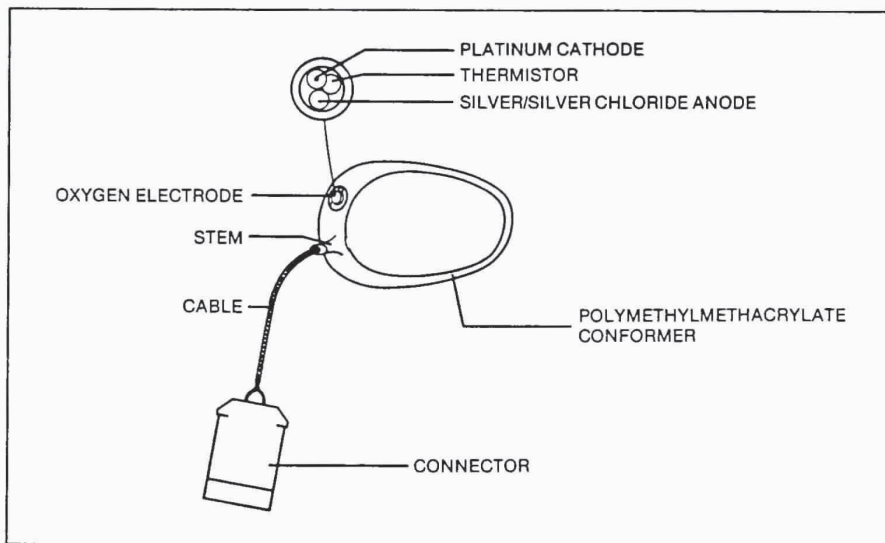


Fig. 10.19 Diagram of the palpebral conjunctive (eyelid)  $pO_2$  sensor.

The conformer ring of the conjunctival sensor has been modified by several researchers to demonstrate the feasibility of using the inner eyelid as a potential site for monitoring blood pH, and  $\text{SaO}_2$  in addition to  $\text{pO}_2$ . Markle and Fink<sup>88</sup> have incorporated a fiber optic pH sensor which has been developed by Peterson et al.<sup>14</sup> into the conformer ring and demonstrated that tissue pH can be measured in normal adult volunteers. Wong et al.<sup>93</sup> have encapsulated a pH-ISFET and a miniature Ag/AgCl reference electrode into the conformer ring and showed that the sensor can be used to follow variations in blood pH in dogs. Mendelson<sup>94</sup> has incorporated a miniature optical reflectance  $\text{SaO}_2$  sensor and demonstrated that the palpebral conjunctiva is also a feasible location for monitoring arterial blood  $\text{SaO}_2$  in rabbits.

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