In Situ Monitoring

Jocelyn M. Hicks

In situ monitoring has been increasingly accepted during the past five years. This approach has been applied to measurement of gas tensions such as \( pO_2 \) and \( pCO_2 \), to pH and ions, to the assessment of jaundice by measurement of bilirubin, and to analysis for \(^{14}\)CO\(_2\) after administration of labeled antipyrine and aminopyrine, for evaluation of hepatic damage. Various techniques have been developed for in situ monitoring: transcutaneous measurements, implantable sensors, ingestible radio-sensitive pills, and breath analysis. Here I review some of these approaches and their limitations. These limitations include the sparsity of circumstances under which the technique can be applied and the probable increase in health-care costs.

Additional Keyphrases: blood gases · bilirubin · pH · radio-sensitive pills · pediatric chemistry · glucose · drug metabolism

Dramatic advances in technology allow clinical monitoring of important physiological measurements by noninvasive techniques. This newer approach to measurement is generally referred to as "in situ" monitoring, i.e., in "the normal or natural place or confined to the site of origin."

Most of the reported studies involving in situ monitoring have been done on pediatric patients or have been animal experiments.

Measurement of blood gases and bilirubin in neonates by transcutaneous methods have now been well described (1-4). Determinations of pH, potassium, and glucose by in situ methods have also been described (5-7). Hepatic drug metabolism has been noninvasively assessed by breath analysis (8).

Other techniques such as analyses done on samples of hair, skin, and nails are noninvasive, but the tests are not done at the patient's bedside and so do not qualify as in situ monitoring.

\[ pO_2 \]

In the eighteenth century, Abernathy (9) was the first to observe that gas exchange takes place through the human skin. In the nineteenth century, Gerlach (10) demonstrated that it was possible to measure elimination of both carbon dioxide and oxygen via the skin. But it was not until 1956 that a transcutaneous electrode for measurement of oxygen was developed (11). By the late 1970s and early 1980s, transcutaneous monitoring of oxygen had become established as a clinical tool in the management of neonates in the intensive care unit.

Transcutaneous measurement of oxygen tension is based on the linear relationship between this measurement and arterial oxygen tension (Figure 1). The oxygen tension of skin is proportional to the arterial oxygen tension only when hyperemia is present, so it is important to hyperperfuse the skin. Commercially available instruments use heat to achieve this. The transcutaneous oxygen electrodes that are now used are in essence Clark electrodes (11) that have been miniaturized and redesigned. The electrode consists of a ring-shaped silver anode, heated by a coil to provide local hyperemia. There are three narrow platinum cathodes, arranged in a triangle. The electrodes, covered by a Teflon and cellophane membrane (Figure 2), are placed on the skin.

According to Cassady (2), several factors are essential to achieve good correlation between \( pO_2 \) and transcutaneous \( pO_2 \): proper sensor preparation and application, appropriate comparisons, a system permeable to oxygen, maximum hyperemia, and no interfering agents. Table 1 lists causes of poor correlation (2).

Transcutaneous measurements of oxygen are also influenced (Figure 3) by normal infant activities such as crying, feeding, and diapering (13-15). Moreover, common activities such as feeding or pulmonary toilet, tracheal suctioning, skin puncture, or arterial blood collection will cause changes in \( pO_2 \); however, the use of transcutaneous monitors dramatically minimizes the need for some procedures, such as blood collection (17).

Transcutaneous monitoring of oxygen clearly is more precise than alternative methods. For example, Peabody et al. (12) showed that both the number of apneic episodes and
their duration were greater when observed by transcutaneous monitoring than by simple observation or by use of cardiorespiratory monitors—e.g., 179 episodes lasting 3057 s vs 487 incidents of 6211 s.

$p_{\text{CO}_2}$

Kost et al. (18) pioneered the evaluation of the use of transcutaneous $p_{\text{CO}_2}$ electrodes. In their recent paper (18) they demonstrated the use of such electrodes in premature babies with respiratory acidosis, persistent fetal-type circulation, or respiratory distress syndrome. Figure 4 illustrates results of a 2-h monitoring session in a premature infant with respiratory acidosis. This case well illustrates fluctuations in $p_{\text{CO}_2}$ that could be missed by discrete sampling.

The second case illustrated (Figure 5) is an example of transcutaneous $p_{\text{CO}_2}$ monitoring in persistent fetal circulation. The measurement of $p_{\text{CO}_2}$ in this way was designed to decrease arterial $p_{\text{CO}_2}$, thereby improving pulmonary blood flow. Because $p_{\text{CO}_2}$ increased on the second day, this infant could not be taken off the respirator. The trend of increasing $p_{\text{CO}_2}$ was finally reversed, and on the third day the baby was extubated. This case illustrates how it would have been possible to follow this case without making invasive measurements of $p_{\text{CO}_2}$ in arterial or capillary (skin-puncture) blood.

When transcutaneous $p_{\text{CO}_2}$ determinations are used, several factors should be kept in mind. For example, unlike the case of $p_{\text{O}_2}$, in all reported cases, transcutaneous $p_{\text{CO}_2}$ exceeds arterial $p_{\text{CO}_2}$. This may be due in part to the heated electrode, which increases the $p_{\text{CO}_2}$ tension. Other factors may include skin metabolism and local trapping of $p_{\text{CO}_2}$ under the electrode. Kost et al. (18) also found significant drift and recommended that monitoring be done in relatively short sessions. In our neonatal unit we have also detected drift when using $p_{\text{CO}_2}$ monitors. Finally, with either $p_{\text{O}_2}$ or $p_{\text{CO}_2}$ monitors, one has to be careful in using heated electrodes, especially with immature infants, whose skin is sensitive and fragile.

The ideal electrode for transcutaneous measurements would be one with which $p_{\text{O}_2}$, $p_{\text{CO}_2}$, and pH could be monitored simultaneously. Until that is available, the use of arterial or capillary blood for these analyses will continue.

### Table 1. Causes of Poor Correlation of Values for Transcutaneous $p_{\text{O}_2}$

<table>
<thead>
<tr>
<th>Causes of poor correlation</th>
<th>In sensor</th>
<th>In infant</th>
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<tbody>
<tr>
<td>Requirements for good correlation</td>
<td>Membrane</td>
<td>Site not changed often enough</td>
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<tr>
<td>Proper sensor preparation and application</td>
<td>Air bubbles</td>
<td>Failure to correct for lag time</td>
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<td></td>
<td>Zeroing solution retained</td>
<td>Inaccurate blood-gas measurements</td>
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<td></td>
<td>Thickness/character incorrect for electrode size</td>
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<td></td>
<td>Electrode</td>
<td>Thick skin</td>
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<td></td>
<td>Calibration error</td>
<td>Scarring</td>
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<td></td>
<td>Surface damage during cleaning</td>
<td>Edema</td>
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<td></td>
<td>Cable broken</td>
<td>Pressure ischemia</td>
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<td></td>
<td>Sensor off skin</td>
<td>Shock</td>
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<tr>
<td>Appropriate comparisons</td>
<td>Membrane thickness or permeability mismatched to skin character</td>
<td>Anemia</td>
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<tr>
<td>System permeable to oxygen</td>
<td>Temperature $&gt; 43.5 \degree \text{C}$</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Maximum hyperemia</td>
<td>Halothane present/ $\text{N}_2\text{O}$ present</td>
<td>Tolazoline</td>
</tr>
<tr>
<td>No interfering agents</td>
<td>From Cassady (2), by permission.</td>
<td></td>
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**Fig. 2.** Diagram of a transcutaneous $p_{\text{O}_2}$ monitor

Cutaway view of electrode: (1) platinum cathode; (2) silver anode (surrounds cathode); (3) electrolyte chamber; (4) cuprophane spacer; (5) polypropylene membrane; (6) O-ring; (7) heating element; (8) NTC-resistor; (9) epoxy resin; (10) retaining ring. From JW McDowell and WH Thiede (Chest 79:355–355, 1980) by permission.

**Fig. 3.** Variation in transcutaneous $p_{\text{O}_2}$ during changes in the patient's condition

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Fig. 4. Management of respiratory acidosis by transcutaneous $PCO_2$ monitoring
In this diagram, both transcutaneous $PO_2$ and $PCO_2$ were followed. Monitoring was begun at point A. Because the $PCO_2$ appeared high, the ventilatory rate was adjusted to bring the $PCO_2$ to acceptable values (B). At point (C) the patient was suctioned, which produced simultaneously a pronounced decrease in transcutaneous $PCO_2$ (D) and an increase in $PCO_2$ (E). Suctioning was then discontinued, and the ventilator was adjusted to reduce $PCO_2$ and increase $PO_2$ (F). At the end of the session $PCO_2$ had dropped from 64 to 44 Torr and the pH had increased from 7.13 to 7.31. From Kost et al. (ref. 18), by permission.

Fig. 5. Persistent fetal circulation: transcutaneous $PCO_2$ monitoring
From Kost et al. (ref. 18), by permission.

Bilirubin

Bilirubin measurements are important in identifying neonatal jaundice and in avoiding kernicterus by appropriate treatment. Frequently it is the rate of increase of bilirubin that is important rather than the absolute value.

Analyses for bilirubin are notoriously difficult; accuracy and precision seem hard to attain (19). There are significant differences between results by different methods (20), and bilirubin concentrations in serum decrease in the presence of light. In addition, many methods give inaccurate results if the samples are hemolytic (20).

Until the advent of transcutaneous monitoring, there were only two methods for estimating bilirubin in vivo. In the early part of this century the only way to assess jaundice was by observation of skin color. In the 1970s a reflectance meter was introduced for measurement of bilirubin (4). Since then, many studies have evaluated the assessment of bilirubin concentration by use of transcutaneous monitors (21–24).

 Serum bilirubin per se cannot be measured by a transcutaneous monitor. The transcutaneous bilirubin measurement is simply an index of the yellowness of the skin and subcutaneous tissues, as measured by reflectivity at 460 and 550 nm.

Kenny et al. (25) recently evaluated these bilirubin monitors. They examined the correlation between the skin bilirubin index (SBI) and serum bilirubin measurements, sources of error in SBI use, quality-control mechanisms that increase the reliability of measurements, and the usefulness of serial SBI measurements in estimating serum bilirubin concentrations. They studied bilirubin measurements in neonatal patients in whom bilirubin was determined for various purposes, including the efficacy of phototherapy, monitoring toward reactions to blood transfusions, and the evaluation of possible sepsis. In addition, they used adult volunteers to determine the precision of the monitors and to see if hematomas affected bilirubin values.

They used several sites for study, including the center of the forehead, above either eye, over the ribs of the chest, and the upper back. Studies of precision of the bilirubin meter for samples from adult volunteers showed a coefficient of variation of 3.4%, which is similar to values reported by other authors. Several sources of error were noted, including probe disinfection and a non-90° angle of contact between the probe and the test surface. Also, measurements in the presence of a hematoma were falsely high. Finally, the response of the meters did not provide values equivalent to bilirubin concentration: The bilirubin must be measured in serum along with the first SBI determination to evaluate the relationship between the two results; this factor then must be applied to all future SBI measurements on a particular patient.

The possible effect of skin melanin on the bilirubin measurement was examined by comparing SBI measurements made with a transcutaneous monitor with measurements of total bilirubin in serum of whites, blacks, and Orientals (Figure 6). The relative errors for the three groups were very similar, although the measured value for the SBI was higher in blacks than in other ethnic groups. Hanne-mann (21) found a lower correlation for blacks than for whites. Others (22) have found it difficult to use the SBI to assess serum bilirubin in infants who are receiving phototherapy. Another factor that has to be taken into account when observing the SBI is the cephalo-caudal progression of dermal icterus (24); i.e., the SBI decreases from the forehead to the sole of the foot.

Obviously, there continue to be difficulties with transcutaneous measurements of bilirubin, difficulties that need to be resolved by further studies. Unquestionably, the availability of noninvasive bilirubin assays would be an asset to any neonatal unit.
Several approaches to measuring pH at the patient's bedside have been described. Earlier attempts depended on pH probes that require a surgical incision (26). Roche Diagnostics has recently developed a probe that allows continuous monitoring of pH. Its use in adults has been described by Rithalia et al. (27), who noted good correlation between tissue pH and arterial pH; they found the electrode to be reliable and easy to handle and the measurements very stable.

In 1968 Jacobson and Mackay (28) devised a "radio pill" that contains a reference pH cell and a telemetry circuit. More recently, Colson et al. (6) described the use of such a pill for long-term measurements of pH (Figure 7), the signal being received by a heterodyne receiver. They used these radio-sensitive capsules to monitor the pH throughout the gut in children with pancreatic disease and to measure the pH at the duodenal-jejunal flexure so as to optimize antacid therapy in adults.

Many children with cystic fibrosis have little or no pancreatic function. A near-neutral pH in the duodenum is essential for breakdown of exogenous proteins. These authors monitored pH after the radio pill passed through the pylorus. They found that in patients with no pancreatic dysfunction, the transition to neutrality was very rapid, whereas in patients with poor pancreatic function, the transition to neutrality was slow, taking as long as an hour. This appeared to be the cause for the concomitant intractable watery diarrhea, which had persisted for 13 years in one patient with cystic fibrosis.

The use of the radio pill is most effective in optimizing antacid therapy. In a patient with hypersecretion of acid, aspirated samples of gastric juice varied greatly in pH, depending on the time interval between the administration of therapy and the aspiration.

Use of radio-sensitive pills for the measurement of pH and other ions may become more important as more research is done on them. For example, the decline of tissue pH with tumor growth and the increase of pH with tumor regression could be of interest in this regard.

**Glucose**

Not only must diabetics monitor their glucose concentrations, they also must take action to keep these values within acceptable limits. A glucose sensor could assist in such control, either by sounding an alarm to warn of impending or existing hypo- or hyperglycemia, or by being part of a system continuously controlling the infusion of insulin by means of a pump.

Lerner et al. (7) described two types of glucose sensor, one enzymic and the other catalytic. In the enzyme type of sensor, glucose oxidase (EC 1.1.3.4) is used to catalyze the oxidation of glucose by oxygen to form gluconic acid and hydrogen peroxide, the concentration of either of which is measured with a metal electrode. The advantage of this approach is the specificity of glucose oxidase for glucose; disadvantages are the relatively short half-life of the enzyme at 37 °C and the instability of the oxygen-sensitive electrode.

The catalytic-type sensor is based on the use of a metal electrode to catalyze directly the electrochemical oxidation of glucose. Lerner et al. conducted their experiments in vitro, using simulated physiological conditions and noting the effects of varying the concentrations of urea and amino acids. They found excellent response for measurements of current in the 200- to 600-mV range for several hours, but over longer periods the reproducibility became poor. They also observed the operation of the glucose sensor in an ultraltrate of bovine serum and found no interferences with the glucose response of the sensor. These encouraging results support the belief that this type of catalytic sensor has potential for in vivo use in diabetic patients.

**Hepatic Drug Metabolism**

Vessell (8) has reported on the aminopyrine breath test to predict hepatic capacity to metabolize drugs. A subnormal rate of elimination of the products of administered [14C]aminopyrine or [14C]aminopyrine in the breath also suggests diminished clearance of administered drugs. The products of

![Fig. 6. Transcutaneous bilirubin in patients of different ethnic backgrounds](image)

From Kenny et al. (ref. 25), by permission

![Fig. 7. Diagram of the pH-sensitive radio pill](image)

From ref. 6, by permission

![Fig. 8. Percentage of administered 14C excreted as 14CO2 in breath 2 h after oral administration of 14Caminopyrine to patients with various liver diseases](image)

Heavy lines and shaded areas indicate mean ± 2 SD
hepatic antipyrine metabolism reflect three different reactions by which antipyrine is metabolized. Similarly, products of hepatic aminopyrine metabolism represent a single metabolic reaction. Vessell suggested that both antipyrine and aminopyrine could thus be used as indicators of liver disease.

As early as 1975, Hepner and Vessell (29) showed that aminopyrine clearance was markedly decreased in cirrhosis, hepatitis, cancer of the liver, and cholestasis (Figure 8).

One might think that, with the availability of the newer techniques for measuring drug concentrations, the breath test approach would be superfluous, but questions still remain concerning drug metabolism. For example, there is often poor correlation between the activities of certain enzymes in serum—e.g., aspartate aminotransferase (EC 2.6.1.1) and alkaline phosphatase (EC 3.1.3.1)—and alterations in drug metabolism. Further, not all drugs are similarly affected by liver disease and not all drugs can be measured at present.

Alcohol

Breath analysis for alcohol can be considered as another form of in situ monitoring, but will not be covered by this review.

The possibility of performing important laboratory analyses by in situ monitoring is exciting. This technology offers the advantage of a noninvasive approach—particularly important in children, for whom multiple skin-punctures can be traumatic. The physiological advantage of in situ monitoring is that changes can be followed as they occur and in the appropriate place. The disadvantages of in situ monitoring are that it can be expensive: several monitors may be required on each patient unit rather than a single instrument in a central laboratory. In addition, frequently a separate monitor is required for each analysis. Obviously important in the use of these monitors is quality control, which would be better carried out under the supervision of clinical chemists from the clinical laboratory.

As one might say of me that I have made a collection of other people's flowers, having provided little of my own but the cord to bind them together.

Montaigne, Essays, book III, chap. XII

References