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This information is current as of June 12, 2013.
Evaluation of a dual-function pH and P\textsubscript{CO\textsubscript{2}} in vivo sensor

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The right external jugular vein and right common carotid artery were exposed and cannulated. The jugular vein was used as a route for the administration of drugs and intravenous solutions. Blood samples were drawn from the carotid artery. A B-D Longdwell catheter-needle (Becton, Dickinson, Rutherford, NJ) (14G, 21/4 in.) was inserted percutaneously into each femoral artery and secured in place with a skin suture (14G was used because the sensors were handmade and subject to size variation). Seldan adaptors (Becton, Dickinson) were attached to the ends of the intra-arterial catheters. High-pressure tubing connected the sidearms of the Seldan adaptors to a Cobe SMS-5 stopcock manifold (Cobe Laboratories, Denver, Colo.). A pressure infusor bag containing heparinized saline (2,000 units/liter) in line with a Sorenson flush unit (Intraflo, Sorenson Co., Salt Lake City, Utah) was attached to another port on the manifold. A Statham pressure transducer was also attached to the Sorenson flush unit. This system allowed systemic arterial pressure to be monitored from either arterial catheter and, if the pressure was damped, the catheter could then be flushed. Temperature was monitored using an esophageal temperature probe. ECG was monitored using needle electrodes in a standard three-lead configuration. Systemic arterial pressure, temperature, and ECG were displayed on a General Electric monitoring system.

The blood gas tensions and pH of the arterial blood samples were determined using a Radiometer pH meter 27GM pH and blood gas analyzer set at a temperature of 37°C. Blood samples were drawn into heparinized plastic syringes and analyzed immediately. The percent hematocrit was determined hourly. The percent hematocrit was determined hourly. Base excess was determined from the P\textsubscript{CO\textsubscript{2}}, pH, and hematocrit using a Siggaard-Andersen nomogram.

The sensor (Fig. 1) is a miniature multiple electrode system similar in construction to the General Electric P\textsubscript{CO\textsubscript{2}} sensor (6) which consists of a PdO (palladium oxide) hydrogen ion-sensing electrode and an Ag/AgCl reference electrode coated with a thin layer of bicarbonate solution and enclosed with a gas-permeable silicone polycarbonate copolymer membrane, the tip portion of which is also permselective for hydrogen ions. For P\textsubscript{CO\textsubscript{2}} measurement, the enclosed PdO/Ag/AgCl electrode system measures the change of pH in the bicarbonate solution which is in CO\textsubscript{2} equilibrium with the blood or solution being measured. The CO\textsubscript{2} from the blood diffuses through the membrane and dissolves in the internal bicarbonate electrolyte forming H\textsubscript{2}CO\textsubscript{3} which subsequently dissociates into H\textsuperscript{+} and HCO\textsubscript{3}-.

From the Henderson-Hasselbalch equation and the electroneutrality law, it can be derived that the pH of the internal electrolyte solution is linearly proportional to the negative logarithm of P\textsubscript{CO\textsubscript{2}}.

For pH measurement, an additional reference electrode outside the sensor but in contact with the blood is required. The measured voltage potential between the Pt/PdO wire and the external reference is a linear function of the pH of the solution measured.

The H\textsuperscript{+}-permselective membrane at the tip portion of the sensor, about 2 cm in length, is now part of the sensing
mechanism. The membrane is made up of copolymer elastomers containing about 60% polysiloxane and 40% poly(bisphenol-A) carbonate. A mobile H⁺ carrier, p-octadecyloxy-m-chlorophenylhydrazonemesoxalonitrile (OCPH), is added to provide the H⁺ permselectivity (2). When placed between two solutions containing different H⁺ concentrations, H⁺ transport occurs with exchange of H⁺ at the two membrane/solution boundaries, similar to I⁻⁻-sensitive glass electrodes, giving rise to an electrochemical potential difference across the membrane which has a near-Nernstian slope characteristic, The slope characteristic of the pH sensor approximates the slope characteristic observed with glass electrodes of 61.54 mV/pH unit at 37°C. The measured potential $E_{PH}$ across the membrane between the PdO electrode of the sensor and the external silver chloride reference electrode can be expressed as

$$E_{PH} = E^\circ + \frac{RT}{F} \ln \left( \frac{[H^+]_{int}}{[H^+]_{ref}} \right) + E_{Ref}$$

where $E_{Ref}$ the half-cell potential of the external reference, is a constant. $E^\circ$ is the standard half-cell potential of the Pd/PdO electrode, and is a linear function of the logarithm of the H⁺ concentration of the internal electrolyte, $[H^+]_{int}$

$$E^\circ = E_{PdO} + E_{M} + E_{Ref}$$

where $E_{Ref}$, the half-cell potential of the external reference, is a constant. $E_{PdO}$ is the half-cell potential of the pH-sensing PdO electrode, and $E_{M}$ is the pH membrane potential and can be expressed as

$$E_{PdO} = E^\circ + \frac{RT}{F} \ln \left( \frac{[H^+]_{int}}{[H^+]_{ref}} \right)$$

thus measuring the pH variation where constant, is a summation of all the constants.

Bicarbonate ion concentration can also be measured directly with the sensor. The measured potential $E_{HCO_3^{-}}$ between the internal and external silver-silver chloride reference electrodes is given by the following equation

$$E_{HCO_3^{-}} = E_{int} + constant - \frac{RT}{F} \ln \left( \frac{[H^+]_{int}}{[H^+]_{ref}} \right) + E_{Ref}$$

where $E_{int}$ and $E_{Ref}$ are the half-cell potentials of the internal and external silver chloride electrodes, respectively, and both are constant. Both the H⁺ concentration and the carbon dioxide partial pressure are related to the bicarbonate concentration of a solution by the equilibrium constant $K$, where

$$K = (H^+) \cdot (HCO_3^{-}) \cdot aPco_2$$

$a$ is the solubility coefficient. Since the bicarbonate ion concentration of the internal electrolyte of the sensor, $[HCO_3^{-}]_{int}$, is not changed, and as CO₂ comes to equilibrium inside the sensor, Eq. 5 becomes

$$E_{HCO_3^{-}} = E^\circ - \frac{RT}{F} \ln \left( \frac{[HCO_3^{-}]_{int}}{[HCO_3^{-}]_{ref}} \right)$$

where $E^\circ$ is a summation of all the constants, thus giving rise to a direct measurement of bicarbonate concentration from the mV output of the sensor.

The sensor was inserted intra-arterially through the end of the Seldon adapter and intra-arterial needle. The external reference electrode, placed in line with the saline-filled catheter between the Seldon adapter and the pressure infusor bag, was a Ag/AgCl electrode with an agar-gel salt bridge of composition 0.024 M NaHCO₃ and 0.15 M NaCl. A Ag/AgCl skin electrode, i.e., the General Electric Daisy electrode, may also be used but it was felt that a reference electrode directly in contact with the blood would produce a more stable reference potential.

The procedure for evaluation of the dual-function sensor (Fig. 2) was divided into five parts over a 7-h period. 1) Initial stabilization period: systemic arterial Pco₂ was maintained at approximately 40 mmHg and pH at 7.40. During this period, the sensor was inserted and calibrated in vivo to agree with the Pco₂ of a blood sample analyzed using the bench instrumentation. If required, the Pco₂ electrode was recalibrated 30 min after the initial calibration.

A method of in vitro sensor calibration is also possible. With this method, the sensor is equilibrated in a chamber perfused with a gas mixture of known CO₂ concentration for 24 h. The sensor is then inserted into a heated calibration port on the CO₂ amplifier module and calibrated to correspond to the calculated Pco₂ of the perfusion
IN VIVO pH AND PCO₂ MEASUREMENT

FIG. 2. Procedure for evaluation of dual-function sensor.

chamber. In vivo calibration was chosen for this study because all subsequent comparisons of systemic arterial pH and PCO₂ were to be made between the bench instrument measurements and the in vivo sensor measurements. The pH sensors were also calibrated in vivo, and a slope of 60 mV/pH units was used to determine the H+ activity from the mV output of the electrode. 2) Induced respiratory acidosis and alkalosis: systemic arterial PCO₂ was adjusted to predetermined levels by first increasing the FICO₂ and, second, by hyperventilating the animal with an FICO₂ of 0%. A Veriflo mixing valve (Veriflo Corp., Richmond, Calif.), connected to a tank of 10% CO₂ and O₂ and to a tank of 100% O₂, was used to produce the desired FICO₂. 3) Stabilization period: systemic arterial PCO₂ and pH were maintained at approximately 40 mmHg and 7.40, respectively. 4) Induced metabolic alkalosis and acidosis: systemic arterial PCO₂ was maintained at approximately 40 mmHg, while systemic pH was adjusted to predetermined levels, first, by sodium bicarbonate infusion and, second, by lactic acid infusion. 5) Respiratory alkalosis and acidosis: systemic arterial PCO₂ was again adjusted to predetermined levels by either altering FICO₂ or by hyperventilation.

RESULTS

The pH and PCO₂ determinations measured at 15-min intervals, using the bench instrument and a dual-function sensor, are shown in Fig. 3. The sensor and bench instrument agree closely with each other except for small but consistently lower sensor PCO₂ values than bench instrument PCO₂ values.

In Fig. 4, the average PCO₂ and pH determinations measured at 15-min intervals using the bench instrument are compared to the determinations made using the dual-function sensors. Eight of the ten sensors were studied during the total evaluation period. Of the other two sensors, both in the first animal, one developed an open membrane, as indicated by the sensor fail light on the amplifier unit at 3 h. The second sensor evaluation ended when the animal succumbed to too vigorous a lactic acid infusion at 4 h.

Table 1 is a statistical comparison between bench instrument determinations of pH and PCO₂ and the in vivo determinations. The data were divided into three ranges for both PCO₂ and pH. Both the absolute and algebraic differences between the bench and sensor readings are shown. (Algebraic difference-sensor value < bench instrument value = negative difference; sensor value > bench instrument value = positive difference.) The absolute difference in pH between the two instruments is about equal for measurements below 7.26 and measurements in the range of 7.26-7.55, but increases at the

FIG. 3. Single General Electric sensor vs. bench instrument measurement of blood pH and PCO₂ with respect to time.

FIG. 4. Average of 10 General Electric sensors vs. average of bench instrument measurements of blood pH and PCO₂ with respect to time.
higher pH range. The algebraic difference indicated that the sensor slightly overestimated pH at the lower range and slightly, but not significantly, underestimated pH at the higher pH ranges as compared to the bench instrument. The absolute difference between the sensor and the bench instrument measurements in the range of 7.26-7.55 was about twice that observed from 166 duplicate pH measurements of blood samples using a Radiometer BMS 3 and the pH meter 27 GM (0.023, SD 0.021, SE 0.0016). The combined results of the differences between the paired sensor measurements of pH in each of the five animals were less than the differences between the bench instrument measurements and the sensor measurements for all three ranges of pH.

The data, in addition to being grouped by range, were also separated into three groups with respect to time: 1) first period of respiratory acidosis and alkalosis and the second stabilization period; 2) period of metabolic alkalosis and acidosis; and 3) the second period of respiratory alkalosis. The differences between the sensor and bench instrument measurements in the second or third groups were not significantly different from those observed in the first group when subdivided in this manner. The sensor, therefore, measured Pco2 and HCO3- equally well in the presence of a HCO3- deficit or a HCO3- excess as in the presence of a normal HCO3- concentration. The sensors, therefore, also functioned as well after 6-7 h as they did during the earlier hours of the experiment.

The absolute difference in Pco2 between the bench instrument and sensor increases with increasing Pco2. This increase, as indicated by the algebraic difference, is predominately from an underestimation of Pco2 by the sensor as Pco2 increases. The absolute difference between the bench instrument and the sensor in the approximate range of 31.50 was slightly less than twice that observed from 150 duplicate Pco2 measurements of blood samples using a Radiometer BMS 3 and the pH meter 27GM (2.38 ± 2.63 SD and ± 0.21 SE). The combined results of the differences between the paired sensor measurements of Pco2 in each of the five animals were approximately equal to the differences between the bench instrument measurements and the sensor measurements, except at the higher range of Pco2, where the paired sensor differences were less.

Variations of systemic arterial pH synchronous with ventilation were observed. The response time of the pH sensor was approximately 0.1 s, and the response time of the Pco2 sensor was approximately 15-30 s. Table 2 shows a comparison of the HCO3- concentration determined from the mV output of the sensor and the HCO3- concentration derived from the bench instrument pH and Pco2 determinations. Also shown is a comparison between the HCO3- concentrations derived from the sensor Pco2 and pH determinations and those derived from the bench instrument determinations. The differences between the bench instrument and the sensor instrument HCO3- measurements were approximately the same using either method (mV output or derived) of determination. Both also showed an increased difference at increased HCO3- concentrations.

**DISCUSSION**

A newly developed dual-function pH and Pco2 sensor was evaluated in this study. Considerable variation between the sensor and bench measurements of pH and Pco2 was observed for some of the sensors, whereas the variation between the sensor and bench instrument measurements was less (i.e., Fig. 3) for other sensors. Part of this variability resulted from the fact that these sensors were constructed by hand. With proper quality control, it should be possible to construct most of the sensors to function as well as, if not better than, the best sensors studied.

A number of other factors, which were not related directly to the electrode construction, also contributed to the difference in the measurements of pH and Pco2 between the bench instrument and the sensor. In some instances, differences between the bench instrument and the sensor measurements were associated with a damped systemic arterial pressure tracing which was also recorded from the arterial needle through which the sensor was placed. Flushing the catheter improved both the sensor measurements and the dynamic response of the systemic arterial pressure tracing. Also, erratic pH sensor measurements were observed if an air bubble developed in the saline reference line.

The method of calibration of the sensor may also have contributed to the difference between the bench instrument and sensor measurements of pH and Pco2. The sensor should be allowed to stabilize either in a chamber perfused with gas containing 4% CO2 or in the animal for at least 30 min before being calibrated for Pco2 measurements. In this study, the sensor was calibrated at 30 min and recalibrated at 1 h, if required. No further recalibration was done. If the sensor required recalibration at 1 h and the bench instrument was in error, then this error was present throughout the remainder of the experiment. Because of the logarithmic nature of the gain of the sensor, the error was exaggerated at higher levels of Pco2. A slope of 60 mV/1 pH unit was used to determine the pH from the mV output of the sensor. This slope was determined in vitro as an approximate slope. Some variability in slope, both in vitro and in vivo, was observed. This would give rise to deviation in low and high pH range away from the calibration point. Sampling errors, such as air bubbles or excess heparin in the syringe and delay in analyzing the sample, also contribute to the difference between the in vivo and in vitro measurements. Furthermore, bench instruments do not give a completely accurate measurement of the in vivo Pco2 and pH (4).
Respiratory variations in pH, previously described by Band and Semple (1), were also observed in this study. These fluctuations in pH with respiration were approximately 0.02 pH unit.

Bicarbonate ion concentration did not appear to be detected more accurately from the direct mV output of the sensor than by the derived concentrations from the sensor Pco2 and pH values. With both measurements, the sensor was less sensitive to bicarbonate ion concentration at the higher levels than was the bench instrument. This is partially due to the one-point calibration and also to the semilogarithmic function of the sensor determination of bicarbonate. A similar consistent reduction in sensitivity to Pco2 was observed at the higher levels of Pco2 studied.

REFERENCES