ON-LINE $P_{O_2}$ AND $P_{N_2O}$ ANALYSIS WITH AN IN VIVO CATHETER ELECTRODE

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SUMMARY

A technique was developed for the in vivo determination of $P_{O_2}$ and $P_{N_2O}$ with a catheter electrode using double-pulse polarography. The method was evaluated in dog studies comparing readings from the electrode with those from a mass spectrometer employing an in vivo probe. The oxygen readings obtained from the catheter electrode were also compared with values obtained by conventional blood-gas analysis. Good agreement was observed between the electrode and the mass spectrometer for both $P_{O_2}$ and $P_{N_2O}$. Similar agreement was found between the electrode readings and blood-gas analysis for $P_{O_2}$. In the presence of halothane, the electrode over-read for both $P_{O_2}$ and $P_{N_2O}$; a remedy is suggested. The in vivo electrode provides an effective, less expensive, alternative to the mass spectrometer for the on-line measurement of $P_{O_2}$ and $P_{N_2O}$ in vivo.

METHODS

Principles of $P_{O_2}$ and $P_{N_2O}$ measurements

We have shown recently (Albery et al., 1978; Brooks et al., 1978; Hahn et al., 1979) that, although nitrous oxide is electrochemically inactive on platinum or gold cathodes, both nitrous oxide and oxygen can be quantitatively reduced on silver cathodes. Figure 1 shows a typical current-voltage curve for the reduction of an oxygen-nitrous oxide gas mixture using a silver cathode. Two plateaux are observed, corresponding to the reduction of the two gases. However, since nitrogen is generated as a product of nitrous oxide reduction, the electrode cannot be polarized constantly at $-1.43$ V (with respect to the silver/silver chloride electrode), both components of an oxygen-nitrous oxide gas mixture can be measured linearly. However, since nitrogen is generated as a product of nitrous oxide reduction, the electrode cannot be polarized constantly at $-1.43$ V, as nitrogen bubbles prevent the electrode functioning. This problem can be overcome by applying alternate polarizing voltage pulses of $-0.65$ V and $-1.43$ V to the cathode.

Pulsing principle

The technique of pulsing polarographic electrodes for oxygen measurement has been reviewed by Hitchman (1978), although the method is not applied commonly to blood-gas electrodes. The theory of this technique for flat plane membrane-covered electrodes has been presented by Mancy, Okun and Reilley (1962). The principle is demonstrated in figure 2, where a single polarizing pulse has been applied to the cathode of a polarographic electrode. The lower portion of this figure shows the electrode response. The leading edge of the pulse produces a capacitative charging of the electrical double layer at the cathode surface (shown as the initial spike), and the cathode current then decreases as oxygen is consumed, first
FIG. 1. A polarogram on a silver cathode, showing clear and distinct plateaux for the reduction of oxygen and nitrous oxide.

From the electrolyte layer and then from the plastic membrane. If the pulse is long enough (as in fig. 2) the usual steady-state polarization (steady output current) is produced. The trailing edge of the pulse then produces a discharge of the double layer, seen as a negative spike, and the electrode current returns towards its (zero) quiescent state. A second pulse for nitrous oxide merely repeats this pattern.

After the initial charging period, which lasts a few milliseconds, the electrode current is proportional to oxygen concentration at any given time after the beginning of the pulse (Hitchman, 1978). As seen in figure 2, when the steady state current is reached, the current no longer decreases with increasing time.

The electrodes used in the study reported below were of the neonatal type (G. D. Searle & Co. Ltd, Size 5FG) with an outside diameter of 1.7 mm.

An integrated circuit double-pulse generator, and a dual sample-and-hold unit, were used to apply the required pulse train to the in vivo electrode, and to observe the resultant oxygen and nitrous oxide currents.

The pulse durations were 2.88 s for oxygen reduction, and 3.15 s for nitrous oxide reduction. There was a 0.96-s pause between these two pulses, and the nitrous oxide pulse was followed by a 7.09-s pause. The oxygen and nitrous oxide currents were both sampled 0.1 s before the end of each pulse.
Mass spectrometer

The Centronic Medical Gas Analyser (200 MGA, T. C. Centronic Ltd), with a blood-gas stainless steel catheter attachment (Brantigan, Gott and Martz, 1972; Foëx et al., 1978) was used to provide a continuous record of arterial oxygen, carbon dioxide, nitrous oxide and halothane tensions. Previous work (Foëx et al., 1978, 1979) has shown that this instrument is linear with changes in blood-gas oxygen and carbon dioxide tension, and that $P_{O_2}$ and $P_{CO_2}$ readings obtained with it agree with conventional blood-gas analysis. The mass spectrometer was not used in its “ASC” (automatic sensitivity control) mode, since the sum of the partial pressures of all of the gases in the arterial blood was unknown. The instrument was calibrated in vitro, before insertion of the catheter to the artery, by placing the catheter tip in saline in an Adams tonometer (Adams and Morgan-Hughes, 1967) at 37°C and tonometering the saline with an oxygen-nitrous oxide mixture (50% : 50%). The electrical output from the mass spectrometer was connected to a signal conditioning unit with a digital read out, and the oxygen (mass 32) and nitrous oxide (mass 30) channels were each scaled to read “50 kPa”. Thereafter, the catheter was immediately inserted to the artery.

Animal model

Four dogs were studied. In each dog anaesthesia was induced with pentobarbitone 25 mg kg$^{-1}$ and maintained by supplements of this agent. After endotracheal intubation intermittent positive pressure ventilation was maintained with an Oxford-Penlon ventilator set to deliver a total volume of 40 ml kg$^{-1}$ at a rate of 12 b.p.m. $F_{iCO_2}$ was set at 0.04 and $Fi_{O_2}$ 0.96. The catheter polarographic electrode and the mass spectrometer catheter were inserted to the abdominal aorta via the femoral arteries, and a blood sampling catheter was inserted to the aortic arch via the carotid artery. The dog was chosen as the experimental model because its femoral arteries are large enough to admit the catheters and its haemodynamic responses to anaesthesia are well documented.

Gas analysis and other measurements

Inspired oxygen, carbon dioxide and nitrous oxide were measured with carefully checked flowmeters and halothane was added from a Dräger vaporizer. The inspired halothane concentration was checked with a Hook and Tucker ultra violet halothane meter, and $FI_{O_2}$ with a paramagnetic analyser (Servoxex OA272) (Nunn, 1964). Inspired and expired carbon dioxide were measured with an infra-red carbon dioxide analyser (Capnograph model URAS 4/2WO). The data from the mass spectrometer were recorded on a four-channel pen recorder (Devices M4-120). The current signals from the in vivo electrode were displayed on a Gould Advance OS4000/4001 digital storage oscilloscope, which allowed hard copies of the transient signals to be recorded periodically on a Bryans 29000 A3 X/Y/t recorder. Both the oxygen and nitrous oxide currents were displayed continuously on digital voltmeters.

PROCEDURE

The in vivo electrode was activated by immersion in saline at 37°C in the Adams tonometer, and its linearity was checked by tonometering the saline with oxygen-nitrous oxide mixtures obtained from Wösthoff gas mixing pumps (Model M300/a-F).

After insertion of the mass spectrometer catheter and the in vivo electrode into the femoral arteries, the mass spectrometer $P_{O_2}$, $P_{CO_2}$ and $P_{N_2O}$ values were continuously recorded on the chart recorder. These records were used to define when a steady blood-gas state was reached—usually within 10-12 min of changing the inspired gases.

After the initial steady-state had been reached, arterial blood was sampled for immediate gas analysis and a hard copy record of the in vivo electrode oxygen and nitrous oxide signals was obtained; the oxygen and nitrous oxide signals on the digital voltmeters were noted. Arterial $P_{O_2}$, $P_{CO_2}$ and pH were obtained from standard Radiometer electrodes, which had been carefully checked to ascertain that they were free from either nitrous oxide or halothane interference (Douglas et al., 1978; Evans and Cameron, 1978).

Nitrous oxide was then added to the inspired gas mixture in steps increasing by 10% v/v, and $Fi_{O_2}$ was diminished accordingly. $Fi_{CO_2}$ was adjusted, when necessary, so that the end-tidal carbon dioxide concentration was kept constant at 5.3% v/v. The ventilation was kept constant at all times.

Since only steady state, and not transient, changes were examined in this study, the mass spectrometer was used to define when new steady blood $P_{O_2}$, $P_{CO_2}$ and $P_{N_2O}$ values had been obtained. Readings were then taken from the flowmeters, paramagnetic analyser, carbon dioxide analyser, and from the indwelling catheter systems.

Halothane was not introduced until the end of the nitrous oxide investigation. A 50% oxygen-4% carbon dioxide-46% nitrous oxide inspired gas
mixture was used as a control, and \textit{in vivo} readings were obtained as indicated above. Halothane was then introduced, commencing at 0.5\% v/v. When the mass spectrometer indicated that the blood halothane concentration was constant, the \textit{in vivo} catheter signals were recorded. The halothane concentration was increased in two steps to 0.9\% v/v and 1.2\% v/v, and the data recorded as above.

Finally, the inspired gases were returned to their initial control values ($F_{\text{IO}_2} = 0.96$, $F_{\text{CO}_2} = 0.04$), to check that the \textit{in vivo} electrode had not drifted unduly during the 4 h duration of each experiment.

\section*{RESULTS}

An example of the oxygen and nitrous oxide current signals obtained from one \textit{in vivo} catheter electrode is shown in figure 3. During each of the four experiments, a good correlation was observed between the electrode oxygen current and measured $P_{aO_2}$ obtained by bench blood-gas analysis. Since the electrode output current varied between electrodes depending upon the membrane thickness and the exact diameter of each cathode, the slopes of the current-$P_{O_2}$ relationship differed from experiment to experiment.

A comparison of 37 determinations on four electrodes in four dog studies is shown in figure 4. The electrode oxygen current has been normalized to the individual straight lines in each study, so that each electrode reading is displayed in (normalized) kPa units, rather than nanoamps. The line of identity is also drawn in figure 4, and it can be seen that the actual data points show a good fit to the line of identity, with a correlation coefficient of 0.99.

Since each dog study gave the same general response, the following results examine the details of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{A tracing of the intravascular electrode response to a train of polarizing pulses, showing the electrode current for the oxygen and nitrous oxide concentrations in the blood.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{A plot of normalized \textit{in vivo} electrode oxygen readings against $P_{O_2}$ values obtained from blood-gas analysis of discrete samples. Thirty-seven determinations from four dog studies are shown, together with the line of identity.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{A plot of the intravascular electrode oxygen current, against $P_{O_2}$ values from discrete blood samples obtained at the same time and analysed in a blood-gas analyser.}
\end{figure}
the pulsed electrode oxygen and nitrous oxide response in one study.

**Oxygen response**

Figure 5 shows the relationship between the pulsed electrode current (displayed on the digital voltmeters) and the $P_{aO_2}$ (blood-gas analyser) of the simultaneously sampled arterial blood. A good correlation is shown.

Figure 6 shows the agreement between the simultaneous readings from the pulse catheter electrode and the mass spectrometer.

**Nitrous oxide response**

The agreement between the in vivo electrode nitrous oxide current and the inspired nitrous oxide gas concentration is shown in figure 7. The $F_{iN_2O}$ values were calculated from the inspired oxygen and carbon dioxide values, obtained from the Servomex and carbon dioxide analyser. Similar results were obtained with $F_{iN_2O}$ values obtained directly from the flowmeter settings.

Figure 8 shows a good correlation between the pulsed electrode nitrous oxide current and $P_{aN_2O}$ measured with the mass spectrometer.

**Halothane effect**

When halothane was added progressively to an otherwise constant inspired gas mixture (50% oxygen–4% carbon dioxide–46% nitrous oxide), the oxygen current increased (fig. 9) as did that for nitrous oxide (fig. 10) although rather erratically.
The mass spectrometer showed that $P_{a\text{O}_2}$ and $P_{a\text{N}_2\text{O}}$ were essentially constant during this period and this was confirmed for $P_{a\text{O}_2}$ by measurements on isolated arterial samples. The changes illustrated in figures 9 and 10 were therefore an effect of halothane on the pulsed electrode.

This halothane effect was observed in the three other dog studies, although the exact magnitude depended upon the current sensitivity of each electrode.

**DISCUSSION**

**Pulsing in vivo**

The results have confirmed our impressions from studies *in vitro* (Hahn et al., 1979) that it might be possible to use a pulsed catheter electrode for quantitative *in vivo* $P_{a\text{O}_2}$ and $P_{a\text{N}_2\text{O}}$ measurement. The electrodes have proved to be stable and linear when used in a pulsed mode. Other workers (for example, Lilley, Story and Raible, 1969; Schmid and Maney, 1970) have applied this method to membrane-covered electrodes for the analysis of small concentrations of dissolved oxygen in waste water, but to the best of our knowledge our work is the first application of the pulse technique to *in vivo* catheter electrodes—especially for measuring two separate gas components with the same electrode. Other advantages of pulsing, such as very low oxygen consumption and the independence of the electrode on membrane permeability characteristics, are under investigation in our laboratories. With hindsight, we would not have employed such long time pulses in this study, as very short pulses would reduce the oxygen consumption of the electrode and therefore reduce the flow effect (Rolfe, 1976) for the electrode.

**Oxygen and nitrous oxide analysis**

Figures 5-8 show that both $P_{a\text{O}_2}$ and $P_{a\text{N}_2\text{O}}$ can be measured simultaneously on the same catheter electrode *in vivo*. Evans and Cameron (1978) have quoted that nitrous oxide can seriously interfere with the measurement of $P_{a\text{O}_2}$ in arterial blood samples. However, our results have shown that the combination of the pulsing techniques with a silver cathode allows an investigator to measure either, or both, gas components in the blood phase. The electrode current was measured in absolute units (nanoamps) in this study, but the linearity of the results (figs 5, 6) indicates that it would be possible to scale the oxygen sensor output in kPa or mm Hg, as with standard neonatal oxygen probes.

Although figures 7 and 8 indicate that the nitrous oxide *in vivo* response of the electrode is also linear, it is not possible to calibrate the electrode by withdrawing a blood sample and analysing it with an *in vitro* analyser. Work is proceeding in our laboratories to solve this problem.

The solution to this problem may lie in applying very short pulse times to the electrode, since this should reduce the blood-gas, or stirring, factor to negligible proportions. An electrode could then be calibrated *in vitro*, in water-saturated gas at 37°C, before insertion to an artery.

Pulsed intravascular electrodes will enable the anaesthetist to monitor $P_{a\text{O}_2}$ continuously, without fear of nitrous oxide interference, whether in the operating theatre or intensive therapy unit. The method will also permit the investigator to examine, in detail, the uptake of nitrous oxide by blood, in either animals or humans.

**Halothane effects**

Figures 9 and 10 confirm the findings of others that halothane greatly affects the performance of oxygen electrodes (Severinghaus et al., 1971; Bates, Feingold and Gold, 1975; Dent and Netter, 1976; Douglas et al., 1978; McHugh, Epstein and Longnecker, 1979), and that it often exaggerates grossly the $P_{a\text{O}_2}$ readings. The most recent study by McHugh, Epstein and Longnecker (1979) was confined to platinum and gold cathode electrodes, but the study by Bates, Feingold and Gold (1975) was directed particularly at silver cathode *in vivo* electrodes. Our own results have been confined to silver cathodes, but show that the
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electrode nitrous oxide signal is also affected by the presence of halothane in blood. The magnitude of this effect varied from dog to dog, and from electrode to electrode. The $P_{O_2}$ signal was increased typically by about 15%, when the dog was ventilated with 1.2% halothane.

The conclusion is that it is impossible to measure arterial $P_{O_2}$ accurately in vivo with a silver cathode electrode in the presence of halothane unless the electrode membrane material was impermeable to halothane. Commercial oxygen catheter electrode membranes are obviously permeable to halothane, and a change in membrane material is needed if these electrodes are to be used with halothane anaesthesia.

We are therefore puzzled by the results of Armstrong and colleagues (1976), since they used the Searle electrode to register arterial $P_{O_2}$ during one-lung oxygen–nitrous oxide–halothane anaesthesia and polarized the electrode at $-0.8$ V. We would deduce from our results that there must not only have been a substantial halothane contribution, but also a significant contribution from the rising portion of the nitrous oxide wave, at this polarizing voltage (Albery et al., 1978; Hahn et al., 1979). Our recommendation is therefore that these electrodes should not be used in the presence of halothane anaesthesia, until a halothane-impermeable membrane material is developed for in vivo use.

Studies nearing completion in our laboratories have indicated that the halothane polarographic wave is inseparable from the oxygen wave on silver cathodes.

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REFERENCES


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ANALYSE LINEAIRE DE LA $P_{O_2}$ ET DE LA $P_{N_2O}$ A L'AIDE D'UNE ELECTRODE CATHETER IN VIVO

RESUME
On a mis au point une technique pour la détermination in vivo de la $P_{O_2}$ et de la $P_{N_2O}$ à l'aide d'une électrode cathéter utilisant une polarographie à double impulsion. Cette méthode a été évaluée au cours d'études effectuées sur des chiens, où l'on a comparé les lectures données par l'électrode à celles émanant d'un spectromètre de masse utilisant une sonde in vivo. Les lectures concernant l'oxygène, obtenues à partir de l'électrode cathéter, ont aussi été comparées aux valeurs obtenues par l'analyse normale sang-gaz. On a observé une bonne corrélation entre l'électrode et le spectromètre de masse qu'il s'agisse de $P_{O_2}$ ou de $P_{N_2O}$. On a trouvé une corrélation similaire entre les lectures de l'électrode et l'analyse sang-gaz pour la $P_{O_2}$. En présence d'halothane, les lectures de l'électrode ont été faussées pour la $P_{O_2}$ et la $P_{N_2O}$; et nous suggérons donc un remède à cela. L'électrode in vivo est un moyen efficace et moins onéreux que l'usage du spectromètre de masse pour la mesure linéaire de la $P_{O_2}$ et de la $P_{N_2O}$ in vivo.

$P_{O_2}$ UND $P_{N_2O}$-ANALYSE MIT EINER IN VIVO-KATHETERELEKTRODE

ZUSAMMENFASSUNG
Eine Methode für in vivo-Bestimmung von $P_{O_2}$ und $P_{N_2O}$ mit Katheterelektrode und Doppelpuls-Polarographie wurde entwickelt, und an Hunden versucht, wobei Ableitungen von der Elektrode mit denen eines Massenspektrometers mittels einer in vivo-Probe verglichen wurden. Die Sauerstoffablesungen von der Katheterelektrode wurden auch mit Werten einer konventionellen Blutgasanalyse verglichen. Gute Übereinstimmung wurde zwischen Elektrode, Spektrometer und Blutgasanalyse für $P_{O_2}$ und $P_{N_2O}$ erzielt, während bei Halothan die Elektrode sowohl für $P_{O_2}$ als auch für $P_{N_2O}$ zu hohe Werte angab; Abhilfe wird vorgeschlagen. Die in vivo-Elektrode ist eine wirksamere und billigere Alternative zum Spektrometer für die in vivo-Messung von $P_{O_2}$ und $P_{N_2O}$.

ANALISIS EN SERIE DE $P_{O_2}$ Y DE $P_{N_2O}$ MEDIANTE UN ELECTRODO RECTIFICADOR IN VIVO

SUMARIO
Se desarrolló una técnica para la determinación in vivo de $P_{O_2}$ y de $P_{N_2O}$ mediante un electrodo rectificador y haciendo uso de polarografía de doble pulso. El método se evaluó en estudios efectuados en perros, comparando las lecturas obtenidas del electrodo con las obtenidas mediante un espectrógrafo de masas que utiliza una sonda in vivo. Las lecturas de oxígeno que se obtuvieron mediante el electrodo rectificador se compararon también con los valores obtenidos mediante los análisis convencionales de la sangre, siguiendo métodos gaseosos. Se observó una buena concordancia entre los resultados del electrodo y del espectrógrafo de masas, tanto para el $P_{O_2}$ como para el $P_{N_2O}$. Se encontró una concordancia similar entre las lecturas del electrodo y el análisis gaseoso de la sangre para el $P_{O_2}$. Las lecturas mediante el electrodo fueron excesivas para el $P_{O_2}$ y para el $P_{N_2O}$ cuando se tomaron en presencia de halotano; se sugiere un remedio. El electrodo in vivo provee una alternativa más efectiva y más barata que el espectrógrafo de masas en lo que respecta a las mediciones en serie de $P_{O_2}$ y $P_{N_2O}$ in vivo.