In Vivo Evaluation of Monopolar Intravascular PO₂ Electrodes

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Summary

Ten intravascular electrodes were evaluated on ten rabbits. The mean stabilization time of 118 ± 52 min was excessively long for clinical use. The *in vitro* cal factor was not reproducible nor accurate. The differences between the PO₂ values measured by the electrode and those obtained from intermittent blood samples were within ± 10 mm Hg during the first 12 hr using the *in vivo* calibration after electrode stabilization. After 12 hr, the electrode PO₂ values using the *in vitro* cal factor or based upon the *in vivo* calibration were increased significantly indicating a possible membrane rupture. This occurred more rapidly in the animal experiments than in the *in vitro* studies using a tonometer, suggesting that continuous flow and pressure changes inside of the aorta contribute greatly to mechanical breakage of the membrane. Histologic evaluation indicated the electrode catheter system was thrombogenic at the level of the electrode tip and this thrombogenicity was primarily related to intimal injury caused by the electrode tip movement as a result of flow and pressure changes inside the aorta.

Speculation

In the present configuration, this system is not ready for clinical use due to an excessively long stabilization time, need for frequent recalibrations, and possible injury to the blood vessel wall.

Continuous monitoring of arterial blood PO₂ by intravascular electrodes provides direct and instantaneous information of blood PO₂ even under extreme shock conditions. Several different types of intravascular electrodes have been described and applied previously (2, 3, 5, 6). In contrast to transcutaneous PO₂ monitoring (4) which yields PO₂ information through the skin, intravascular monitoring is invasive, and, therefore, more susceptible to complications related to stability, calibration procedures, and biocompatibility.

The results of the *in vitro* evaluation of four monopolar intravascular PO₂ electrode groups manufactured by International Biophysics Corporation (IBC, Irvine, CA) were reported previously (1). Although the Au-Ag/AgCl electrode combination exhibited the best characteristics, their *in vitro* drift was greater than 10 mm Hg/24 hr.

To further verify the clinical applicability of the Au-Ag/AgCl intravascular electrode combination, ten sensors on ten rabbits were evaluated continuously for 4 days under simulated clinical conditions. Standard IBC sensors were used, and the procedures applied were those suggested by IBC.

The goals of this study were: 1) to establish the relationship between PO₂ values obtained using an intravascular electrode (electrode monitoring, em) and PO₂ values obtained by intermittent determination from blood samples (sample determination,

sd); 2) to evaluate the electrode drift and average recalibration period; 3) to determine the blood compatibility of the electrode.

MATERIALS AND METHODS

ANIMAL PREPARATION AND ELECTRODE PLACEMENT

Ten adult male New Zealand rabbits (2.0-3.5 kg) were anesthetized by iv administration of sodium pentobarbital (25 mg/kg). A 5F Argyle catheter containing a PO₂ electrode was passed subcutaneously through an incision in the animal's back to another incision of the inner aspect of the thigh where the catheter was inserted into the femoral artery up to the level of the descending aorta approximately 2 cm above the diaphragm. The electrode then was advanced such that it protruded approximately 1 cm past the catheter tip. The exact positions of the catheter tip and the electrode were determined at autopsy at the conclusion of the experiment. A thermistor probe was implanted subcutaneously in the animal's back to monitor subcutaneous temperature. Keflin (cephalothin, 63 mg/kg) was administered intraperitoneally after surgical preparation of the rabbit. The animal was confined in a box in a crouching position where it was allowed to recover and where it remained for the duration of the experiment. The restraining box was constructed with provisions to effect FiO₂ changes. The PO₂ in the box was monitored continuously with an O₂ monitor (IMI 3702). A positive pressure flush system was used to flush the catheter with heparinized saline and 5% dextrose (5 units heparin/100 ml blood/hr) at an infusion rate of 6 ml/hr. The flush system with an intravascular catheter PO₂ electrode and an external reference is shown in Figure 1.

Detailed construction of the intravascular PO₂ electrode was previously described (1, 3). The catheter adapter (Fig. 1) was used mainly to secure the electrode position in the catheter, to make a watertight feedthrough seal for the electrode, and to provide a sidearm through which blood samples could be obtained and the catheter flushed. The adapter consisted of a threaded acrylic housing with a sidearm, a tapered catheter fitting, and a silicone rubber gasket. The positioning of the catheter and the watertight seal was accomplished by squeezing the silicone rubber gasket with a mating threaded fitting through which the electrode was passed. Flush solution and blood samples were allowed to pass through a PVC tube connected to the sidearm of the housing.

The reference electrode was a 1" long 0.050" O.D. chlorided silver wire immersed in an electrode well (Fig. 1). The well was made of an acrylic rod drilled to fit a luer lock fitting. The electrode well communicated through two PVC tubes with the catheter adapter (the cathode) and a three-way stopcock where flow control for flushing and blood sampling was utilized.

Blood was transfused intermittently from a donor animal after each cumulative removal of 10% of the animal's total blood volume due to sampling. Blood samples were drawn through a three-way stopcock for bench determination with a blood gas

Fig. 1. External arrangement used with continuous intravascular PO₂ electrode. Left, a complete system; upper right, detail of the reference electrode with well; lower right, detail of a catheter adapter with an electrode positioned through a watertight seal.

analyzer (Corning Model 165). Bench determinations were performed at 37°C and they were corrected for difference between body and analyzer temperature.

DATA ACQUISITION AND PROTOCOL

Electrode current was monitored and recorded continuously through a system which consisted of an IBC Model 145-MPA Differential Oxygen Analyzer, electrode disconnecting switches, a dual-channel chart recorder, and a calibration current source with its associated switches. The disconnecting switches were designed to maintain the polarographic voltage across the electrode while they were disconnected. In this configuration, the current source could be connected to the input of the amplifier for system calibration.

Before electrode connection, the electronic system was calibrated and zeroed. The amplifier's sensitivity (nA/mm Hg PO₂) was set for each electrode according to its "in vitro cal factor" supplied by IBC.

After it was connected to the electronic system, the electrode was allowed to stabilize before evaluating its other characteristics.

After stabilization, an *in vivo* calibration was performed by varying the animal's FiO₂ stepwise to 15, 35, and 50%, each of which was maintained 20 min. Blood samples were taken for bench analysis before each FiO₂ change. The animal's FiO₂ was then restored to room air and bench analyses of blood gases were performed every 2 hr for the next 6 hr. This constituted a cycle which was repeated every 6 hr throughout the 4-day experiment.

After each experiment, autopsy was performed on all animals to determine the exact location of the electrode and catheter tip inside the artery. Samples of the kidney, liver, lungs, and the descending aorta including the catheter and electrode were obtained. The distal end of the vessels contained a suture and the proximal end was marked with India ink. All samples were fixed in 10% formalin for histologic examination.

For histologic examination, the suture was removed, the vessel was grasped firmly between the fingers, and the catheter contain-

Fig. 2. Mean and SD of slope ($\Delta\text{PaO}_{2em}/\Delta\text{PaO}_{2sd}$) as a function of time after electrode stabilization based on the *in vitro* cal factor.

ing the electrode was removed gently. Sections from the distal, mid, and proximal portions of the vessels along with sections of liver, kidney, and lung were submitted in numbered cassettes, processed in a Technicon, and stained with hematoxylin and eosin. Tissue samples from a noncatheterized control rabbit, killed with sodium pentobarbital, were processed in the same manner.

DATA EVALUATION

Stabilization Time. Stabilization time (min) is defined as the time interval between the point when the electrodes were con-

nected to the electronic system and the point when the electrode output varied within ± 5 mm Hg PO₂/hr while the animal breathed room air. This interval specifies the initial period when the electrode cannot be used because of excessive drift.

Correlation between continuous and intermittent PO₂ values. 1) Based on *in vitro* cal factor. The continuous PO₂ values based on the electrode *in vitro* cal factor were fitted by linear regression to the intermittently determined PO₂ values obtained from blood samples.

$$\text{PaO}_{2\text{em}} = C \times \text{PaO}_{2\text{sd}} + B \quad (1)$$

where the subscripts em and sd denote the continuous and intermittent PaO₂ values obtained from the electrode and blood sample, respectively. C represents the slope, and B the intercept.

To obtain an idea of the validity of the *in vitro* cal factor and the electrode drift at physiologic PO₂, the difference PaO_{2em} - PaO_{2sd} at a PaO_{2sd} of 80 mm Hg was calculated from the regression data obtained every 6 hr during the entire run.

2) Based on initial *in vivo* calibration. PaO_{2em} values based on the *in vitro* cal factor were equated to PaO_{2sd} values obtained during the first *in vivo* calibration using the following formula:

$$\text{PaO}_{2\text{em}_{\text{vivo}}} = \text{PaO}_{2\text{em}_{\text{vivo}}} - B/C \quad (2)$$

The relationship between the PaO_{2em} expressed using the *in vivo* cal factor and the PaO_{2sd} was fitted with another linear regression yielding:

$$\text{PaO}_{2\text{em}_{\text{vivo}}} = C_{\text{vivo}} \times \text{PaO}_{2\text{sd}} + B_{\text{vivo}} \quad (3)$$

To obtain an idea of the validity of the *in vivo* calibration and the electrode drift at physiologic PO₂, the difference PaO_{2em} - PaO_{2sd} at a PaO_{2sd} of 80 mm Hg was calculated from the regression data obtained every 6 hr during the entire run.

RESULTS

STABILIZATION TIME

The stabilization times of the electrodes ranged from 69–217 min. The mean was 118 ± 52 min.

Fig. 3. Mean and SD of intercept (PaO_{2em} at PaO_{2sd} = 0) as a function of time after electrode stabilization based on the *in vitro* cal factor.

CORRELATION BETWEEN CONTINUOUS AND INTERMITTENT PO₂ VALUES

Based on *in vitro* cal factor. Figures 2 and 3 summarize the mean slope ($\Delta\text{PaO}_{2\text{em}}/\Delta\text{PaO}_{2\text{sd}}$), intercept (PaO_{2em} at PaO_{2sd} = 0), and their SD calculated from linear regression lines over 72 hr. The slopes at the beginning were less than 1 indicating that the changes in the PaO_{2em} were less than the changes in the PaO_{2sd}.

The slopes initially decreased during the first 24 hr, possibly

Fig. 4. Slope and intercept over a 4-day period (single animal experiment).

Fig. 5. Mean and SD of difference (PaO_{2em} - PaO_{2sd}) at a PaO_{2sd} = 80 mm Hg over a 4-day period based on the *in vitro* cal factor. (Points above the 0 level indicate PaO_{2em} < PaO_{2sd}, points below the 0 level indicate PaO_{2em} > PaO_{2sd}.)

indicating a reduction in membrane oxygen permeability. This was followed by a sharp increase most likely attributable to a partial rupturing of the electrode's membrane.

The large SD both for slope and intercept indicate that the *in*

Fig. 6. Mean and SD of difference ($\text{PaO}_{2\text{em}} - \text{PaO}_{2\text{sd}}$ at a $\text{PaO}_{2\text{sd}} = 80$ mm Hg) over a 4-day period based on the *in vivo* calibration. (Points above the 0 level indicate $\text{PaO}_{2\text{em}} < \text{PaO}_{2\text{sd}}$, points below the 0 level indicate $\text{PaO}_{2\text{em}} > \text{PaO}_{2\text{sd}}$.)

vitro cal factor was not initially accurate nor reproducible to within ± 10 mm Hg. The magnitude and variation of the intercept was greater than ± 10 mm Hg PO_2 indicating that a 2-point calibration is required.

A typical correlation plot depicting changes in slope and intercept over 4 days in a single animal is presented in Figure 4. Mean and SD of the difference between $\text{PaO}_{2\text{sd}}$ and $\text{PaO}_{2\text{em}}$ based on the *in vitro* cal factor at $\text{PaO}_2 = 80$ mm Hg over 4 days is shown in Figure 5. The $\text{PaO}_{2\text{em}}$ values were initially lower than the $\text{PaO}_{2\text{sd}}$ and after 24 hr, they started to increase, again suggesting possible membrane rupture.

Based on initial in vivo calibration. Mean and SD of difference between $\text{PaO}_{2\text{sd}}$ and $\text{PaO}_{2\text{em}}$ based on the initial *in vivo* calibration at a $\text{PaO}_2 = 80$ mm Hg over 4 days is shown in Figure 6. These data indicate that the difference between the $\text{PaO}_{2\text{sd}}$ and $\text{PaO}_{2\text{em}}$ was within 10 mm Hg during the first 12 hr, and that the $\text{PaO}_{2\text{em}}$ showed a significant increase during the remainder of the experiment, again suggesting the possible membrane rupture.

HISTOLOGIC STUDIES

All sections of the aorta contained highly elastic vessels with no smooth muscle detectable with hematoxylin and eosin. All catheterized vessels showed some abnormality. These varied from small attached platelet thrombi proximal to the electrode tip (Fig. 7), to splitting of the internal elastic lamina with and without small attached platelet thrombi at the level of the electrode (Fig. 8), further to large thrombi containing fibrin, erythrocytes, and leukocytes. These large thrombi often filled the lumen leaving only the catheter and electrode "hole" (Fig. 9). Two samples showed internal elastic lamina splitting at the level of the electrode. One sample showed splitting with attached platelet thrombi that were overlaid by large thrombi containing fibrin, erythrocytes, and leukocytes. The youngest portion of the thrombus was adjacent to the electrode tip and contained only erythrocytes and fibrin. No

Fig. 7. Small platelet thrombus proximal to electrode tip. Internal elastic lamina beneath the thrombus is not split. (Aorta, Rabbit 1, medium magnification, hematoxylin and eosin.)

Fig. 8. Internal elastic lamina is split and overlaid by platelet thrombus. Thrombus is beginning to expand by deposition of fibrin and erythrocytes toward lumen. (Aorta, Rabbit 3, medium magnification, hematoxylin and eosin.)

Fig. 9. Large attached thrombus with catheter-electrode hole. Thrombus occludes aorta. (Rabbit 5, low power, hematoxylin and eosin.)

thrombi contained hemosiderin, fibroblasts, or other evidence of chronicity or organization.

The progression of these findings suggest that mechanical injury at the level of the electrode tip starts the thrombotic process that the catheter and electrode wall does not act as the thrombotic nidus.

No thromboemboli were found in liver, kidney, or lung. In one sample, there was a thrombus in the arteriole in the aortic adventitia. This may represent either emboli or extension of the aortic thrombus. Lack of thromboemboli in other organs and the proximity of the aortic thrombus suggests extension. In all except one sample, the thrombotic process was localized and attached to the area of the intimal change adjacent to the electrode tip.

In summary, all catheterized aortas showed changes ranging from internal elastic lamina splitting to massive fibrin-erythrocyte thrombosis at the level of the electrode tip. In this small series, the earliest event was lamina splitting followed by the aggregation of small platelet thrombi over the splitting followed by accumulation of large fibrin-erythrocyte thrombi. The catheter and electrode wall did not appear to act as a nidus for thrombosis. If true, thrombotic complications of this intravascular catheter electrode system could be prevented by eliminating or decreasing the force of contact between the electrode tip and intima, produced by flow and pressure variations inside the aorta.

DISCUSSION

Ten intravascular oxygen electrodes were evaluated on rabbits for 4 days. The results indicate:

1) Stabilization time of 118 ± 52 min is exceedingly long for practical clinical application. Some means of decreasing the stabilization time by electrode pretreatment should be studied further.

2) The considerable deviation of the mean slope C from unity and intercept B from 0 at the first calibration and, thereafter, indicates that the *in vitro* cal factor was neither accurate nor reproducible. This can be attributed to changes in membrane

thickness occurring any time between the *in vitro* factory calibration and the usage of the electrode.

3) Using the *in vivo* calibration after the stabilization of the electrode, data indicate that the $\text{PaO}_{2\text{sd}} - \text{PaO}_{2\text{em}}$ differences were within ± 10 mm Hg during the first 12 hr.

4) After 12 hr of usage, the electrode PO_2 values using the *in vitro* cal factor or based upon the *in vivo* calibration were increased significantly indicating a possible membrane rupture. This significant increase in electrode current occurred more rapidly in animal experiments than during *in vitro* experiments in the tonometer (1). Continuous flow and pressure changes inside of the aorta contributed greatly to mechanical breakage of the membrane.

5) The histologic study indicated that the electrode catheter system was thrombogenic at the level of the electrode tip. The thrombogenicity was due to intimal injury caused by a lack of mechanical fixation of the electrode tip in the catheter and/or catheter in the aorta. These thrombi, although localized, often resulted in the prevention of sample withdrawal.

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