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Ion-Selective Electrodes and Their Clinical Application in the Continuous Ion Monitoring[a]

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INTRODUCTION

Ion-selective electrodes (ISEs) are devices that permit the activity of a given ion in a solution to be determined potentiometrically despite the presence of other ions. The general layout of an ISE cell assembly is given elsewhere.[1,2] A great number of ISEs have been developed and recommended for analytical application.[2] Undoubtedly, the fundamentally different types of membranes offer a host of attractive applications in the field of selective-ion detection,[1,2] yet the potential of liquid membrane electrodes is virtually unlimited.[1] They allow the construction of cell assemblies in a wide variety of shapes and sizes.[1,3] Examples are dip-in macroelectrodes,[3] microelectrodes (tip diameter $\lesssim 1$ μm),[4] catheter electrodes,[5–10] surface electrodes,[11,12] ion-selective field-effect transistors (ISFET),[13–15] flow-through assemblies,[3,15] and potentiometric analysis slides.[16] The neutral carriers especially, defined as ionophores that carry no charge if not complexed by the selected ion, have led to ion-selective electrodes with a large range of selectivities.[1,3] Here we report on the use of neutral carrier–based solvent polymeric membranes[17] for the continuous monitoring of ion activities in whole blood.

OPTIMIZED ION-SELECTIVE ELECTRODES

A clinically relevant application of ISEs imposes severe demands in respect to selectivity, stability of the measured cell potential difference (EMF), response time, and lifetime of the electrodes.[1,3] TABLE 1 indicates a very narrow expected EMF range (column 4) for the specified physiological range (columns 2 and 3) of Na^+, K^+, Ca^{2+}, and H_3O^+. A reasonable resolution within this range demands standard deviations in the EMF measurement smaller than those indicated in column 5 of TABLE 1. In view of this goal, the plasticized polyvinyl chloride membranes presented in TABLE 2 (for

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TABLE 1. Demands Towards Potentiometric Ion Activity Determinations and Related Performance of the Optimized Membrane Electrodes

Ion	Concentration Range (mmol/l)	Activity Range (mmol/l)	EMF Range (mV)	Tolerable Standard Deviation[a] (mV)	Measured EMF Stability[b] (mV)
Na^+	135–150	102–112	2.4	0.12	0.06
K^+	3.5–5.0	2.6–3.7	9.1	0.46	0.11
Ca^{2+}[c]	1.0–1.2	0.34–0.41	2.4	0.12	0.11
H_3O^+	4.3×10^{-5}–5.6×10^{-5}	3.34×10^{-5}–4.35×10^{-5} (pH 7.48–7.36)	6.8	0.35	0.37

[a]For a five-fold subdivision of the given physiological range with a 95% confidence limit.
[b]EMF change of an aqueous calibration solution before and after six hours of continuous measurement in blood of the extracorporeal circulation.
[c]Free ionized Ca^{2+}.

membrane components see FIGURE 1) have been studied in the extracorporeal blood bypass of dogs and rabbits.[18]

RESULTS AND DISCUSSION

The membranes presented in TABLE 2 have been used in a previously described flow-through system.[19] The system was calibrated before and after the contact with blood. Runs lasting six hours or more for the simultaneous continuous measurement of Na^+, K^+, Ca^{2+}, and H_3O^+ in the extracorporeal blood bypass of dogs and rabbits yielded EMF shifts of the calibration solution before and after the run of only 0.06 mV (Na^+), 0.11 mV (K^+), 0.11 mV (Ca^{2+}), and 0.37 mV (H_3O^+).[18] A comparison of columns 5 and 6 in TABLE 1 indicates that the membranes presented in TABLE 2 indeed have the required stability. Therefore there is no need for an intermediate calibration over periods of at least six hours. The selectivity of the membranes is sufficient to avoid corrections for interfering ions present in whole blood.[1,3,18] In permanent contact with whole blood, a continuous-use lifetime of membranes of the type specified in TABLE 2 can be expected to be longer than three months.[1,3,20]

Neutral carrier-based membranes containing valinomycin[23] and tridodecyl amine,[24] respectively, have been used in catheter electrodes. The simultaneous recording of the K^+ concentration and the pH is shown for such electrodes in FIGURE 2. The catheter electrodes of a diameter of about 1 mm were passed into the abdominal aorta of an anesthetized cat via a femoral artery. KCl was then injected via the femoral

TABLE 2. Optimized Membrane Compositions for Continuous Measurement in Whole Blood

Membrane for Ion	Composition [wt. %][a]
Na^+	1.2% ETH 227; 66.3% ETH 469; 32.5% PVC
K^+	1.3% Valinomycin; 68.3% ETH 469; 30.4% PVC
Ca^{2+}	3.3% ETH 1001; 2.1% KTpC1PB; 63.7% ETH 469; 30.9% PVC
H_3O^+	1.0% Tridodecyl amine; 0.5% KTpC1PB; 65.6% ETH 469; 32.9% PVC

[a]See FIGURE 1 for details of components.

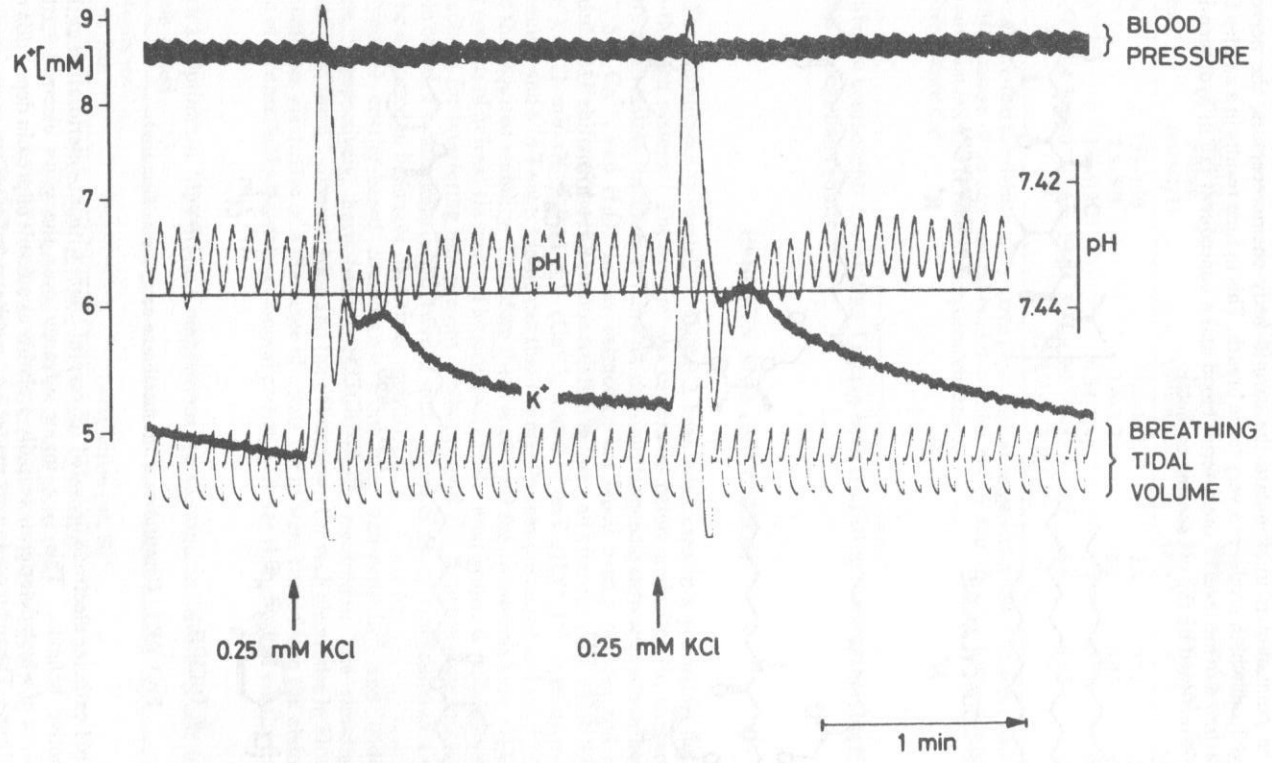

FIGURE 2. Arterial blood K^+ concentration and pH recorded continuously in the abdominal aorta of an anesthetized cat using solvent polymeric membrane catheter electrodes. Arrows indicate addition of 0.25 millimoles KCl.

obtained with a radio-telemeter probe unit.[25] The catheters had separate reference electrodes connected to the blood via saline bridges.

OUTLOOK

The highly selective and reliable potentiometric systems now available for the determination of Na^+ and K^+ metal cations are likely to displace flame photometry in clinical laboratories in the next few years.[3] Neutral carrier-based sensors for a wide variety of other cations (e.g., Li^+),[3] including organic ions, are at hand. Enantiomer-selective systems are entering analytical relevance.[21] Neutral carriers for anions open up a large variety of accessible selectivities for anion-selective sensors.[22]

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DISCUSSION OF THE PAPER

QUESTION: Once the electrode has been placed within the body and left there for a period of time how is the quality of the observations to be monitored?

SIMON: That is definitely a very tricky point because as soon as an ion-selective device is incorporated in an animal, it is very difficult to have any quality control. One suggestion that has been made is that the sensor is introduced using a cannula and then from time to time a blood sample is taken out through that cannula in order to make an independent measurement. That is about the best that can be done at this time. In the future, we should design sensors that are so reliable that we can guarantee decently constant behavior over the time needed, let's say a couple of hours or at some point days. I think we are very close to that. We definitely can guarantee it for ten hours right now.

B. CHANCE (*Johnson Foundation, Philadelphia, PA*): In terms of long term stability the table that you presented didn't give a value that I could readily translate into pH.

SIMON: It is about 0.005 of a pH unit for a period of about six hours without any recalibration.

CHANCE: Is there any flow artifact with these electrodes? When your flow of fluid rapidly passes them what happens?

SIMON: Yes, definitely there is an effect but this effect is not inherent to the membranes as such. The flow potentials we have in these systems can be nicely rationalized just by computing streaming potentials. If we calculate these streaming potentials this matches quite well with what we have. This simply means that the system has to be designed adequately. The flow-through system I showed has been designed so that the streaming potentials do not contribute to any significant level. In our case the streaming potentials computed are on the order of about one microvolt.

CHANCE: I see, so the sinusoidal oscillations that you observed in the heart were definitely not due to any flow artifact.

SIMON: That is definitely right. But may I add it is very easy to make flow-through systems that are extremely sensitive to flow. But if they are designed well this is not the problem. I think a major issue is that these systems have to be shielded, electrically, extremely well. We normally put screens around all the tubing because these may act as antennas and may pick up all kinds of electrical signals from the environment.

J. H. LADENSON (*Washington University, St. Louis, MO*): Are you anticipating a problem when you use an open flowing junction with the material flowing directly into the animal?

SIMON: Yes.

LADENSON: Depending upon how this is going to be used and what size human it may be used in, can you use some alternative to that system?

SIMON: Yes. We use this free-flowing system because it is extremely stable. In using these free-flowing reference junctions we have not observed any significant interference from the liquid junction. Of course if the animal is very small this may lead to a problem if you pump too much electrolyte into it. The flow rate we have chosen is rather large, we could easily reduce it by a factor of about five or ten. It has been used in rabbits, which are relatively small animals. I think the total blood volume is only about 50 milliliters.