Continuous Potentiometric Measurement of Different Ion Concentrations in Whole Blood of the Extracorporeal Circulation

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Introduction

Previous contributions have documented the reliability of potentiometric Na^+ [2], K^+ [3], Ca^{2+} [5], and H^+ [4] activity measurements in blood using liquid membrane electrodes. The usefulness of the membranes was evaluated by comparison with independent methods. Because of the requirement for membrane electrode systems with long lifetimes, the original membranes have been modified by using a novel, highly lipophilic PVC plasticizer. It has turned out that this new non-polar membrane solvent is suited to replace all of the plasticizers previously employed in the Na^+, K^+, Ca^{2+}, and H^+ membranes. In addition to the improved lifetime, an increased EMF stability of the electrodes was observed. The applicability of the four membranes when incorporated in a flow-through electrode system for blood measurements is documented in the light of continuous monitoring in the extracorporeal circulation of animals.

Requirements for Potentiometric Determinations of Ion Activities in Blood

As a consequence of the very narrow physiological ion activity ranges, a series of severe demands are imposed on the ion-selective electrode systems with respect to selectivity and EMF stability. Additional requirements such as adequate response time and electrode lifetime are imposed by the organization of clinical laboratories. Bearing these conditions in mind, the required properties of the membranes and of the electrode measuring system for clinical work are briefly discussed in the following sections.

Selectivity

Using the Nicolsky-Eisenman equation and assuming typical physiological activity ranges, minimal afforded selectivity factors K_{IJ}^{Pot} can be defined as

$$K_{IJ}^{Pot} = \frac{a_{i,low}}{(a_{j,high})^{z_i/z_j}} \frac{p_{ij}}{100}$$

where $a_{i,low}$ = lowest value of the physiological activity range of the ion I^{z_i} to be measured; $a_{j,high}$ = highest value of the physiological activity range of the interfering ion J^{z_j}; and p_{ij} = maximal tolerated error (%) caused by the ion J. A typical worst case

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Table 1. Demands upon potentiometric ion activity determinations arising within the normal physiological ranges

Ion I^{z+}	Concentration range (mM/l)	EMF range[a] (mV)	Tolerable standard deviation[b] (mV)	Proposed ideal standard deviation[c] (mV)
Na^+	135 -150	2.4	0.12	0.06
K^+	3.5- 5.0	9.1	0.46	0.23
Ca^{2+}[d]	1.0- 1.2	2.4	0.12	0.06
H^+	4.3- 5.6×10^{-5} (pH 7.48-7.36)	6.8	0.35	0.18

[a] Calculated on the basis of the Nernst equation according to the corresponding activity ranges.
[b] For a five-fold subdivision of the given physiological range with a 95% confidence limit.
[c] The standard deviation of the EMF measurement should be 10% of the standard deviation s_i of the interindividual mean of the ion concentration (the given EMF ranges correspond to 4 s_i [13]).
[d] Free ionized Ca^{2+}.

study sets $p_{ij} = 1\%$ and assumes that no interfering ions are considered for the electrode calibration (see Fig. 3).

EMF Stability

Although the required EMF stability is mainly dictated by the physiological ranges, recommendations of generally tolerable standard deviations are hardly meaningful since they depend on the guidelines of the clinical laboratories as well as on the nature of the analyses. Two situations are documented in Table 1.

Response Time

Multichannel analyzers are often based on different but quite fast methods of analysis. In order to use ion-selective electrodes in such devices, the electrode response time has to be compatible with the response behavior of the other techniques. Typical measuring cycles of commercial analyzers demand an electrode response time of less than 30 s. Other applications of electrode devices in clinical medicine usually call for an even faster response of the electrode. An impressive example from medical research is the use of H^+-selective catheter electrodes in the aorta of cats for the recording of pH changes which follow the breathing rhythm [11].

Lifetime

The lipophilicity of each membrane component is a very important factor in determining the required lifetime for the membrane electrode. However, the geometry of the membrane and of its vicinity in the electrode body, the sample solution, and the kind of measurement (batch technique, continuous flow) heavily influence the lifetime of the electrode. A detailed discussion in this respect is given for a continuous flow system by U. Oesch et al. [8].

Liquid Junction Potentials

A substantial contribution to the measured EMF differences (e.g., calibration solution compared with sample solution) originates from changes of the potential at the liquid junction between the reference electrolyte of the reference electrode and the sample solution. In routine work, this effect is minimized by the use of a concentrated solution of an equitransferrent electrolyte (e.g., 3 *M* KCl). For some special applications, such as ion-monitoring in the extracorporeal circulation, an isotonic reference solution has to be applied for physiological reasons. If Na^+ is varied in the sample within its extracellular physiological range (135–150 m*M* Na^+), the liquid junction potential will change by 0.07 mV (3 *M* KCl) and 0.5 mV (150 m*M* NaCl reference solution), respectively. The latter case implies that the demands as given in Table 1 would not be fulfilled without additional corrections [6].

Streaming Potentials

Streaming potentials E_s could be responsible for fluctuations in the measured EMF in the case of moving sample solutions in flow-through electrode systems. Theory predicts the highest values of E_s for the combination of small channel diameter, high flow velocity, low electrical conductivity of the sample, and large distance between ion-selective and reference electrode [7, 12]. These parameters are comparable for the flow-through electrode system discussed here and for typical commercial analyzers. For such arrangements, an insignificant contribution of E_s to the measured EMF of $< 1\ \mu V$ is calculated [7].

Properties of the Ion-Selective Membranes and of the Flow-Through Electrode System

A previously described [1, 9, 10] flow-through electrode system has been used in a slightly modified version (Fig. 1) in order to demonstrate the clinical relevance of potentiometric H^+, Na^+, K^+, and Ca^{2+} determinations.

The flow-through electrode modules are manufactured from polymethylmethacrylate blocks and interconnected by means of PTFE cones or silicone rubber O-rings. The membrane solution (40 µl of a solution of 180 mg membrane material in 2 ml tetrahydrofuran) is introduced into the module via the opening for the uptake of the internal filling solution, the sample channel being plugged by Teflon tubing. In order to regulate the temperature and to eliminate electrostatic field interference, the whole flow-through arrangement is mounted inside a grounded aluminum block. For further elimination of electrostatic charging effects, the plastic pump covers are contacted with metal screens. All PTFE tubing is sleeved with wire mesh, and the screens, the mesh, and the aluminum block are grounded. When the ion-selective membrane and the reference electrode are replaced by resistors of 56 MΩ and 270 kΩ, respectively, the stability of the electronic components is ± 0.025 mV (standard deviation $N = 100$) over a period of 24 h.

The new membranes (Fig. 2) have been incorporated together in the flow-through electrode system (Fig. 1). In Fig. 3, measured selectivity factors are compared with

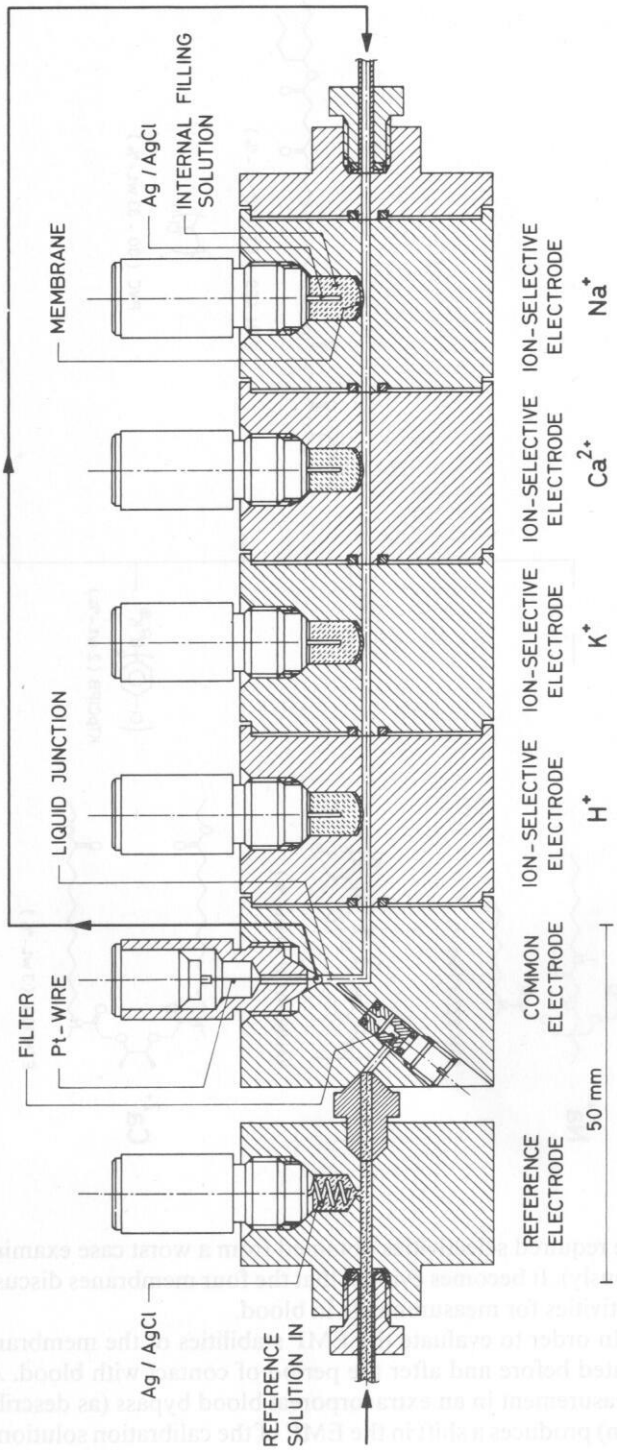

Fig. 1. Schematic cross section of the flow-through electrode system

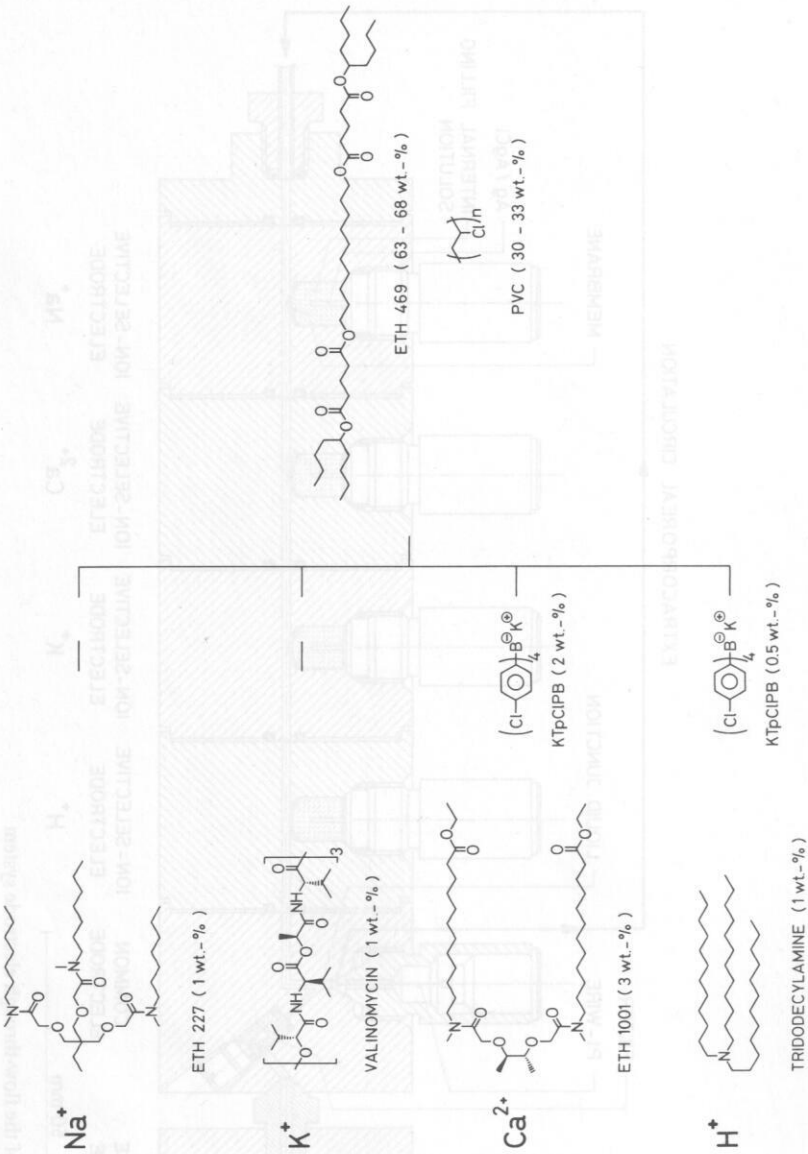

Fig. 2. Constitution of the membrane components and composition of the liquid membranes discussed

the required selectivities obtained from a worst case examination (as discussed previously). It becomes evident that the four membranes discussed exhibit adequate selectivities for measurements in blood.

In order to evaluate the EMF stabilities of the membranes, the system was calibrated before and after the period of contact with blood. About 6 h of continuous measurement in an extracorporeal blood bypass (as described in the following section) produces a shift in the EMF of the calibration solution before and after the run

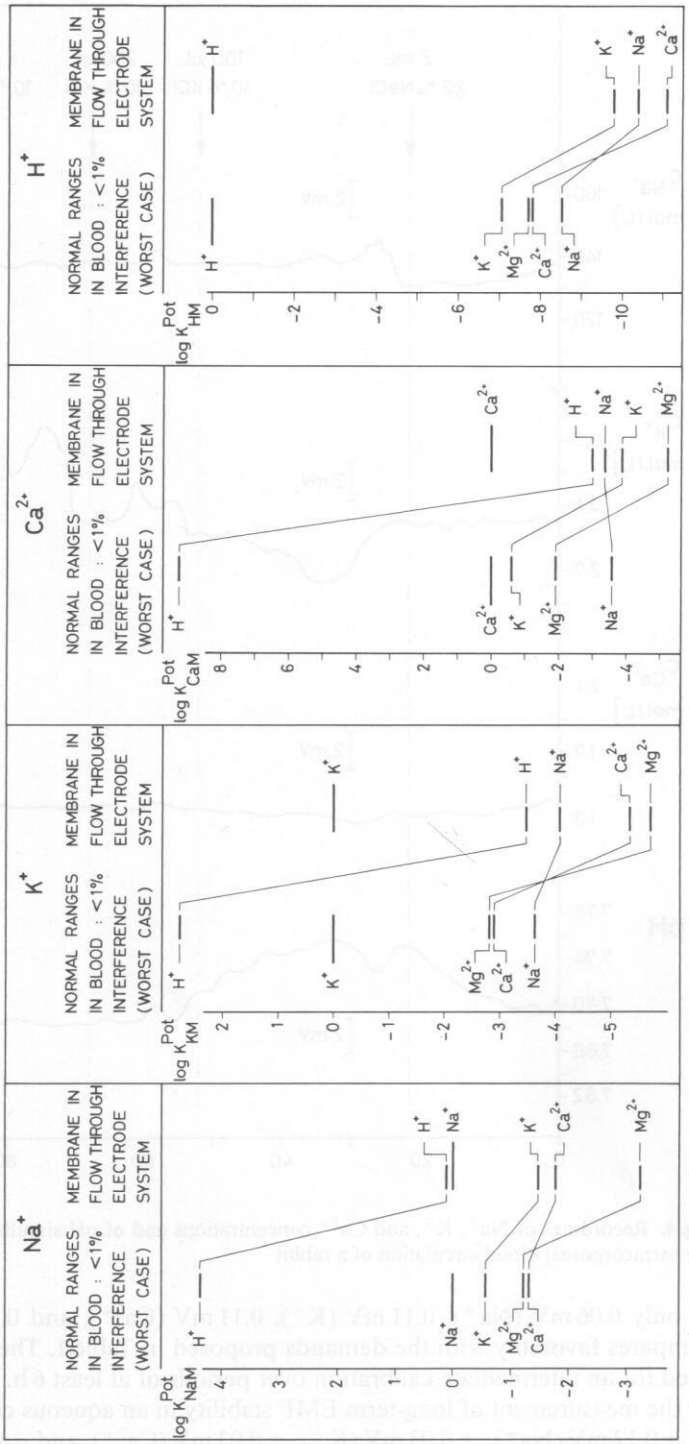

Fig. 3. Required *(left-hand columns)* and measured selectivity factors *(right-hand columns)*

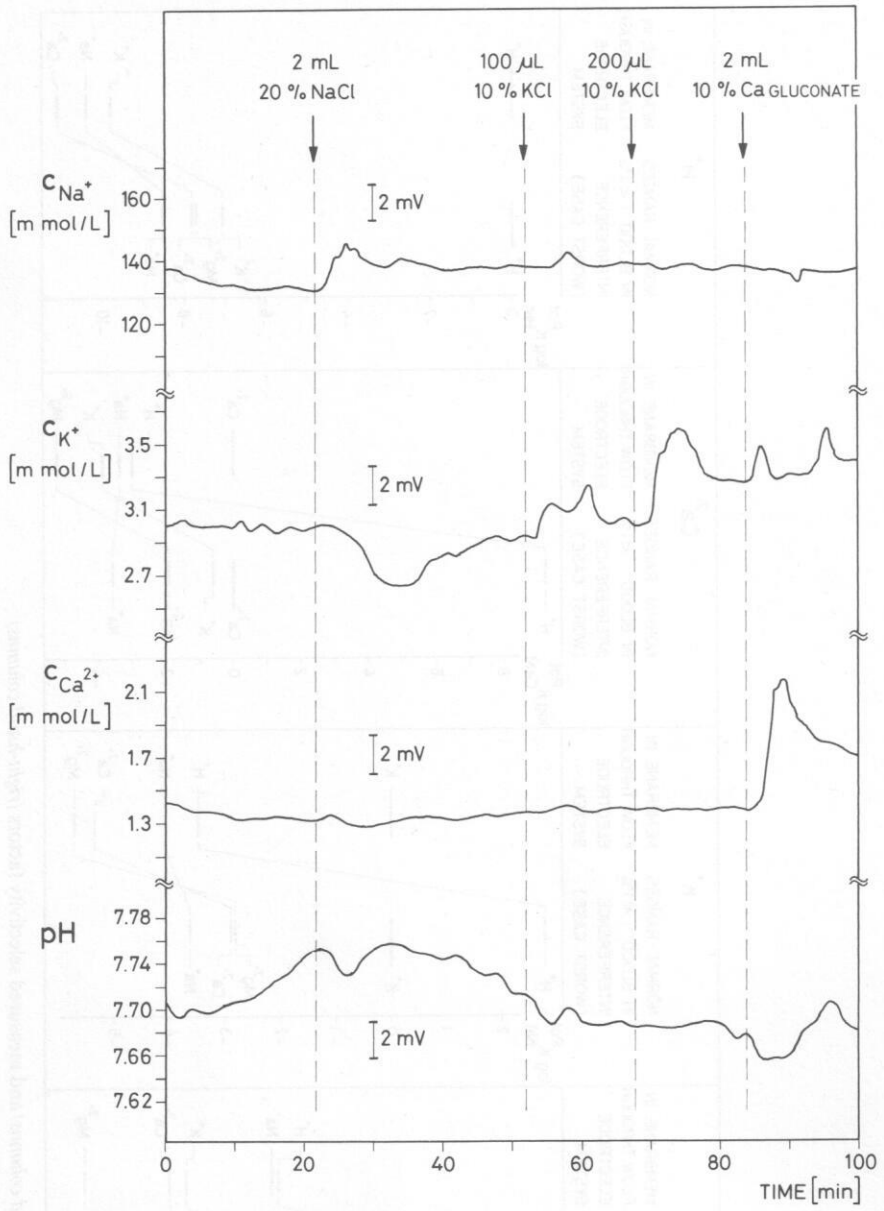

Fig. 4. Recordings of Na^+, K^+, and Ca^{2+} concentrations and of pH simultaneously measured in the extracorporeal blood circulation of a rabbit

of only 0.06 mV (Na^+), 0.11 mV (K^+), 0.11 mV (Ca^{2+}), and 0.37 mV (H^+). This compares favorably with the demands proposed in Table 1. Therefore, there is no need for an intermediate calibration over periods of at least 6 h. This is underlined by the measurement of long-term EMF stability in an aqueous calibration solution of ± 0.12 mV (Na^+), ± 0.03 mV (K^+), ± 0.03 mV (Ca^{2+}), and ± 0.08 mV (H^+) (5 h,

standard deviations, $N=100$). The observed EMF drift was 0.03 mV/h (Na^+), 0.01 mV/h (K^+), 0.01 mV/h (Ca^{2+}), and -0.03 mV/h (H^+). We have no explanation for the slightly poorer Na^+ EMF stabilities as compared with the shift values presented. The reproducibility of the EMF differences ($N=5$) between an aqueous calibration solution and a serum sample was ± 0.05 mV (Na^+), ± 0.10 mV (K^+), and ± 0.09 mV (Ca^{2+}). The value for H^+ is not given because the reproducibility test was carried out under aerobic measuring conditions, thus inducing changes in the serum pH.

Continuous Potentiometric Measurement in the Extracorporeal Blood Circulation

Figure 4 depicts profiles of Na^+, K^+, and Ca^{2+} concentration as well as of the pH simultaneously measured in the extracorporeal circulation of a rabbit. In order to check the electrode behavior different salt solutions were injected intravenously. All four of the membranes proved to be adequate for reliable monitoring of ion concentrations or activities (as already discussed). In a previous report, continuous Ca^{2+} measurement in the bypass of dogs during drug (calcitonin) administration has been discussed [5].

In conclusion, adequate neutral carrier based liquid membranes and measuring devices are now available to perform simultaneous, reliable, potentiometric determinations of Na^+, K^+, Ca^{2+}, and H^+. If the technique is applied invasively (bypass, catheter), some risk persists because of the lack of knowledge on the contamination of blood by the membrane components [8], the sterilization procedure, thrombus formation, and the immune response.

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