Conductivity measures coupled with treatment with ion-exchange resin for the assessment of sodium concentration in physiological fluids: analyses on artificial solutions

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Abstract. In humans, sodium is essential for the regulation of blood volume and pressure. During hemodialysis, sodium measurement is important to preserve the patient from hypo- or hyper-natremia. Usually, sodium measurement is performed through laboratory equipment which is typically expensive, and requires manual intervention. We propose a new method, based on conductivity measurement after treatment of dialysate solution through ion-exchange resin. To test this method, we performed in vitro experiments. We prepared 40 ml sodium chloride (NaCl) samples at 280, 140, 70, 35, 17.5, 8.75, 4.375 mEq/l, and some “mixed samples”, i.e., with added potassium chloride (KCl) at different concentrations (4.375-17.5 mEq/l), to simulate the confounding factors in a conductivity-based sodium measurement. We measured the conductivity of all samples. Afterwards, each sample was treated for 1 min with 1 g of Dowex G-26 resin, and conductivity measured again. On average, the difference in the conductivity between mixed samples and corresponding pure NaCl samples (at the same NaCl concentration) was 20.9%. With treatment with the resin, it was 9.9%, only. We conclude that ion-exchange resin treatment coupled with conductivity measures may be a possible simple approach for continuous and automatic sodium measurement during hemodialysis.

1. Introduction
In humans, sodium is essential for the regulation of blood volume and blood pressure, as well as osmotic equilibrium and pH. In advanced renal failure, sodium balance becomes positive and the extracellular volume expands, and this leads to adverse cardiovascular consequences in patients under hemodialysis (HD) treatment. Thus, the maintenance of the sodium balance is an essential role of chronic HD treatment. As a consequence of a negative or positive sodium gradient between dialysate and plasma, patients can receive an even excessive removal of plasma sodium (leading to hypotensive events), or on the contrary may otherwise experience sodium gain [1]. Thus, reliable measurement of sodium concentration during HD is clinically relevant.

Currently, there are two main approaches for sodium measurement during HD: flame photometry or ion-selective electrode method [2]. These methods are based on medical instruments, such as the hemogas-analyzers, which are not integrated with the HD machine. Thus, the measurement of sodium (and, possibly, other variables) always requires manual intervention by an operator. In addition, the measurement performed by these instruments is typically very expensive.
The aim of this study is to propose an approach for possible simple, not expensive, and automatic measurement of sodium during HD. Our approach is based on conductivity measurement coupled with the use of a ion-exchange resin. Conductivity measurement of plasma, dialysate or ultrafiltrate sample alone cannot provide a highly accurate estimation of sodium concentration, though it should be recognized that the main contribution to conductivity of such samples is in fact due to sodium. However, coupling the simple conductivity measurement with treatment of the samples through appropriate ion-exchange resin can lead to improved accuracy, since the effect of the disturbing factors (especially, other cations) is reduced. In this study, we focus on the presentation of our approach applied to artificial samples.

2. Methods

2.1. Samples of sodium chloride and potassium chloride solutions

We prepared some artificial samples, at different sodium and potassium concentration, based on the following considerations. The sodium concentration in plasma is around 140 mEq/l; the concentration of the other cations, which represent the main confounders for conductivity-based sodium measurements, are around 4-5 mEq/l for potassium and calcium, and 1.5 mEq/l for magnesium [3]. In the analysis of the artificial samples, we assume for simplicity that the main confounder is potassium, and neglect the effect of the other cations. Deionized water (18.5 MΩ × cm resistivity, Millipore MilliQ Element system, USA) and sodium chloride (NaCl, >99.5%, Sigma-Aldrich, Italy) was used to prepare a 500 ml sample of NaCl solution at 280 mEq/l, that is, a concentration value certainly including the highest physiological plasma values (being twice the typical value). Afterwards, through dilution process, we obtained other six samples at lower concentrations, reaching the typical concentration values of plasma potassium and calcium (140, 70, 35, 17.5, 8.75, 4.375 mEq/l).

With the same process, with water and potassium chloride (KCl, >99.0%, Sigma-Aldrich) we prepared samples at the same concentration of the sodium samples (i.e., from 280 to 4.375 mEq/l). We also prepared some “mixed” samples (i.e., containing both sodium and potassium), in this case by direct weighting of the appropriate amount of NaCl and KCl for each sample. Specifically, we prepared a total of nine mixed samples: NaCl at 280 mEq/l and KCl at 17.5, 8.75, 4.375 mEq/l; NaCl at 140 mEq/l and KCl at 8.75, 4.375 mEq/l; NaCl at 70 mEq/l and KCl at 8.75, 4.375 mEq/l; NaCl at 35 mEq/l and KCl at 4.375 mEq/l; NaCl at 17.5 mEq/l and KCl at 4.375 mEq/l (see also Table 1). Such mixed samples were prepared to simulate the presence of a confounding factor (i.e., potassium in this case) for the measurement of sodium concentration in the sample. Of course, depending on the sodium concentration value of the samples, we selected some significant but appropriately lower concentrations of the confounding factor, thus somehow mimicking what would happen in biological samples (see typical physiological plasma ion concentrations reported above).

2.2. Conductivity measures and resin treatment

We performed impedance measurement of the samples through a Solartron 1260 impedance analyzer (Solartron Analytical, UK) [4]. Briefly, through the Solartron 1260 we applied a 100 mV r.m.s. voltage to the outer couple of electrodes of the measurement probe (SP06T model, Delta OHM, Italy), which was immersed into the glass tube containing the analyzed sample. The electric current was measured through the inner electrodes of the probe. We analyzed the impedance of the samples in the 10^3–10^7 Hz range, but in this study we simply considered the impedance value at 1 kHz, as done in several commercial conductivity meters. From the impedance, we then derived conductivity, considering that the geometrical factor of the probe (k-factor) was equal to 0.7 cm^-1. For each measure, we used 40 ml of the solution sample of interest. For each sample studied, we performed two independent measures, and took the average conductivity values between the two measures. All the impedance measures were performed with the samples at ambient temperature (20 °C with maximum variations of ±0.3 °C). In a first set of experiments, we measured the conductivity, as described above, in all the prepared samples. In a second set of experiments, we introduced the use of a ion-exchange
resin, i.e., the Dowex G-26 exchange resin (Dow Chemical Company, USA). This is a uniform particle size, strong acid cation-exchange resin. Such resin acts replacing the cation species in a solution with hydrogen ions, H⁺. However, specially strong affinity is expected for the alkali metals, and with sodium in particular. Thus, the use of the resin should determine variations in the characteristics of analyzed solution samples that are related to the sodium concentration. In this second set of experiments, we immersed different quantities of resin in a 40 ml sample of NaCl at 140 mEq/l. Specifically, we tested the effect of 1, 2, 3, 4 g of resin. For each quantity of resin, we stirred the sample solution through an electromagnetic micro-stirrer (Velp Scientifica, Italy) for 1 min. Afterwards, the resin was separated by the sample solution, and conductivity measure of the sample was performed. Subsequently, with 1 g of resin, we tested over the 140 mEq/l NaCl sample the effect of changing the contact time: in fact, we increased the time to 5, 10 and 20 min. Based on the results obtained in the second set of experiments, we proceeded with a third set of experiments. In this phase, each of the prepared samples, which underwent conductivity measure in the first set of experiments, was treated with 1 g of resin for 1 min, and hence conductivity measure was again performed.

3. Results

The conductivity of the NaCl samples (with concentration from 280 to 4.375 mEq/l) was essentially linear ($R^2=0.99$, $P<0.0001$), as shown in Figure 1, top. Similar trend was shown by the KCl samples ($R^2=0.99$, $P<0.0001$), Figure 1, bottom.

![Figure 1. Relationship between concentration and conductivity before (circle) and after (square) resin treatment for NaCl (top) and KCl (bottom). Regression equations are also reported.](image-url)
In the analysis of the effect of the resin on the sample conductivity, we tested the conductivity variation of the NaCl sample at 140 mEq/l with 1, 2, 3 or 4 g of resin, with a contact time of 1 min. The conductivity difference (before and after resin treatment) was $\Delta = 15.1$, $\Delta = 20.9$, $\Delta = 24.8$, $\Delta = 26.3$ mS/cm, for 1, 2, 3, 4 g, respectively. It can be concluded that, for the volume of our sample (40 ml), increasing the quantity of resin over 1 g determines an increase of the resin effect, but the effect is already clearly evident at 1 g. We also tested the changes in resin effect due to variations in the contact time between the resin and the sample. With the NaCl sample at 140 mEq/l, and with the use of 1 g of resin, we found $\Delta = 16.8$, $\Delta = 19.4$, $\Delta = 20.1$ mS/cm, for 5, 10, 20 min, respectively. We concluded that the use of 1 g of resin, with a contact time of 1 min, provided a clear resin effect, thus it was sufficient for the treatment of our 40 ml samples.

The conductivity of the NaCl samples, and of the KCl samples, treated with 1 g of resin for 1 min, was still essentially linear ($R^2=0.99$ and $R^2=0.98$, $P<0.0001$ for both), as reported again in Figure 1. At any concentration, the resin effect was clearly evident for both NaCl and KCl samples. For each concentration value it was possible to quantify the resin effect as the pre-post resin conductivity difference, normalized to the conductivity of the sample before resin treatment. For the NaCl samples, the resin effect was $1.43 \pm 0.08$ (mean±standard error), whereas for the KCl samples it was $1.21 \pm 0.13$: this was a demonstration of the stronger effect of the resin on sodium rather than on potassium.

We then analyzed the mixed samples, containing both NaCl and KCl at different concentration values, to simulate the presence of a confounding factor (i.e., potassium) for the measurement of sodium concentration of the sample. For each mixed sample, we computed the percentage difference in conductivity between the mixed sample and the corresponding pure NaCl sample, at the same NaCl concentration (for instance, the conductivity difference between the 280 mEq/l NaCl + 17.5 mEq/l KCl sample and the pure 280 mEq/l NaCl sample, normalized to the latter, etc.). We named such difference $\varepsilon$, since it is an estimation of the error in the conductivity-based estimation of sodium concentration, due to the presence of the confounding factor (potassium). First, we computed $\varepsilon$ before the resin treatment (Table 1). Afterwards, we treated the mixed samples with the resin (1g for 1 min), and calculated $\Delta_{\text{pre-post}}$: i.e., the conductivity difference before and after the resin treatment. Again, we computed $\varepsilon$ values as explained above, this time based on the pre-post resin conductivity differences (Table 1). It can be noticed that, for each mixed sample, the $\varepsilon$ values were always lower when the pre-post resin conductivity differences were considered: in fact, on average, $\varepsilon$ without resin treatment was 20.9%, whereas it was 9.9% with resin treatment. This means that, in the analyzed artificial samples, the treatment with resin reduced the confounding effect of other ions (potassium, in this case) on the assessment of sodium concentration, based on conductivity measurement approach.

| Table 1. Concentration (mEq/l) of mixed samples (NaCl+KCl), and corresponding difference $\varepsilon$ in the conductivity (%) compared to the samples with NaCl alone at the same concentration, without resin treatment, and with resin treatment (pre-post resin conductivity difference). |
|---------------------------------|----------|----------|----------|----------|----------|
| NaCl $\rightarrow$ KCl $\downarrow$ | 280      | 140      | 70       | 35       | 17.5     |
| Pre-treatment                   |          |          |          |          |          |
| 17.5                            | $\varepsilon_{\text{pre}} = 17.28$ | -         | -         | -         | -         |
| 8.75                            | $\varepsilon_{\text{pre}} = 15.27$ | $\varepsilon_{\text{pre}} = 19.93$ | $\varepsilon_{\text{pre}} = 31.53$ | -         | -         |
| 4.375                           | $\varepsilon_{\text{pre}} = 12.78$ | $\varepsilon_{\text{pre}} = 13.09$ | $\varepsilon_{\text{pre}} = 20.54$ | $\varepsilon_{\text{pre}} = 24.09$ | $\varepsilon_{\text{pre}} = 33.13$ |
| Post-treatment                  |          |          |          |          |          |
| 17.5                            | $\varepsilon_{\Delta_{\text{pre-post}}} = 6.35$ | -         | -         | -         | -         |
| 8.75                            | $\varepsilon_{\Delta_{\text{pre-post}}} = 7.45$ | $\varepsilon_{\Delta_{\text{pre-post}}} = 7.07$ | $\varepsilon_{\Delta_{\text{pre-post}}} = 12.83$ | -         | -         |
| 4.375                           | $\varepsilon_{\Delta_{\text{pre-post}}} = 2.94$ | $\varepsilon_{\Delta_{\text{pre-post}}} = 0.41$ | $\varepsilon_{\Delta_{\text{pre-post}}} = 17.13$ | $\varepsilon_{\Delta_{\text{pre-post}}} = 23.07$ | $\varepsilon_{\Delta_{\text{pre-post}}} = 11.71$ |
4. Discussion and conclusion

We proposed an approach, based on conductivity measures and resin use, which may contribute to possibly overcome the current limitations in the measure of sodium during HD. Conductivity measure of ultrafiltrate for sodium determination has been recently proposed by the company Bellco, Italy (http://www.bellco.net/public/files/Right_Therapies_News.pdf), based on the hypothesis that the main contribution to conductivity is in fact due to sodium. However, simple conductivity measurement of the ultrafiltrate cannot provide highly accurate estimation of sodium concentration, due to the presence of several disturbing factors: especially, the other cations (potassium, calcium, magnesium), but also glucose [5]. The main novelty of this study is in fact the idea of coupling the simple conductivity measures with treatment of the solution sample with a not expensive (~0.04 € per gram) acid cation-exchange resin, which can reduce the effect of the disturbing factors in sodium determination. In fact, the contact of the solution with the resin determines an “amplification” of the sample conductivity, which depends mainly on the sodium concentration, due to the resin special affinity with sodium. As a consequence, in the conductivity-based determination of the sodium concentration of the sample, resin treatment allows reducing the effect of the disturbing factors. It should be noted that, in our experiments, for simplicity we assumed potassium as representative of any possible disturbing factor. In any case, the other disturbing factors should have lower effect on resin behavior, as previously discussed. In conclusion, we have proposed an approach for possible simple, automatic and not expensive measurement of sodium during a HD session. Further studies, on patients in different clinical conditions, are necessary to prove the actual possibility of integrating the proposed method on a HD machine.

References

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