Online measurement of hemodialysis adequacy using effective ionic dialysance of sodium—a review of its principles, applications, benefits, and risks

Shakil ASLAM,1 Subodh J. SAGGI,2 Moro SALIFU,2 Robert J. KOSSMANN1

1Fresenius Medical Care of North America, Renal Therapies Group, Waltham, Massachusetts, USA; 2Division of Nephrology, State University of New York-Health Sciences Center at Brooklyn, Brooklyn, New York, USA

Abstract
Dialysis dose is an important determinant of clinical outcomes in patients with end stage renal disease on maintenance dialysis. In clinical practice dialysis dose is monitored at least monthly by urea clearance based on Urea Kinetic Modeling. Online clearance monitoring using effective ionic dialysance (EID) of sodium (Na+) is available on some hemodialysis machines. This paper reviews the background, methodology, additional applications, and potential risks associated with EID. Effective ionic dialysance provides a reliable, real-time, noninvasive, and inexpensive measurement of dialysis dose during an ongoing hemodialysis (HD) session to allow interventions and assess the impact of these changes on clearance. Surveillance of vascular access flow rates can be used to screen for access dysfunction and refer for interventions. There is a concern that EID measurements may cause Na+ loading because of high dialysate Na+ used during these measurements, however, mathematical models, in vitro experiments, and clinical studies in patients on maintenance HD do not show any evidence of Na+ loading during EID measurements. We cannot rule out the possibility of nonosmotic Na+ accumulation in the skin because no published literature exists on this topic as it pertains to clearance measurements based on EID of Na+.

Key words: Adequacy of dialysis, effective ionic dialyance, K\textsubscript{ecn}, EID, salt loading

INTRODUCTION
Dialysis dose is an important determinant of outcomes in patients with end stage renal disease (ESRD) on

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In clinical practice dialysis adequacy is monitored by $\text{spKt/V}_{\text{urea}}$ only once a month assuming that the same dose of dialysis will be delivered for all treatments if the dialysis prescription is not changed between treatments. However, the data from HEMO study showed that 21% of the patients prescribed a target $\text{spKt/V}$ of 1.3 had $\text{spKt/V}$ of less than 1.2 at any given time. More frequent measurements of $\text{spKt/V}_{\text{urea}}$ may be more useful, however, these may not be practical due to the cost and effects of frequent blood draws in this patient population. In addition, these measurements do not inform the clinicians of real time clearance data to allow adjustment of the prescription during an ongoing HD treatment.

Currently two different technologies are available for assessment of dialysis dose “Online” in real time. Ultraviolet (UV) spectroscopy based systems such as Adimea (B. Braun, Hessen, Germany) and Dialysis Dose Monitoring (Diascan, Nikkiso, Tokyo, Japan) which measure absorbance of the spent dialysate to estimate dialysis dose and effective ionic dialysance (EID) of Na\textsuperscript{+} based methods such as Diascan by Baxter, Deerfield, IL, USA, and Online Clearance Monitoring (OCM\textsuperscript{TM}) and Online Clearance (OLC\textsuperscript{TM}) by Fresenius Medical Care, Waltham, MA, USA.

Although, UV absorbance of the spent dialysate is not specific for urea, Castellarnau et al. reported a correlation of 0.93 between blood urea-based $\text{Kt/V}$ and Adimea $\text{Kt/V}$ in a study of 64 subjects. They reported that factors that reduce dialyzer clearance caused an overestimation of $\text{Kt/V}$ and proposed ways to address this issue. Other factors such as food intake during HD have also been reported to cause errors in the UV absorbance-based clearance estimates but not in the EID-based methods.

EID of Na\textsuperscript{+} based methods are the focus of this review which discusses the background, methodology, other applications, and the potential risk of Na\textsuperscript{+} loading associated with the use of this technology.

The principles and methodology of EID-based clearance measurement

Dialysis clearance measurement using EID or effective conductivity clearance ($K_{\text{ecn}}$) of Na\textsuperscript{+} was described in detail by Polascheg in 1993. This method uses a transient increase in the dialysate conductivity (represented mostly by dialysate Na\textsuperscript{+}) to 15.5 mS/cm (dialysate Na\textsuperscript{+} of 155 mEq/L, approximately) to measure its diffusion across the dialyzer membrane. As a result of diffusion of Na\textsuperscript{+} into the blood due to this high dialysate to blood gradient, the dialysate conductivity drops at dialyzer outlet. This change in conductivity as compared to the baseline conductivity is used to derive conductivity clearance. Since, the dialysate conductivity is mostly determined by its Na\textsuperscript{+} content the conductivity clearance is considered to be equivalent to Na\textsuperscript{+} clearance. There are two protocols for measurement of EID. These methods differ in how conductivity pulse is applied to measure $K_{\text{ecn}}$. In machines equipped with OLC, available on Fresenius 2008 K2 and later models, $K_{\text{ecn}}$ is measured by first increasing the dialysate conductivity to 15.5 mS/cm for 2 to 3 minutes followed by reduction in the dialysate conductivity to 13.5 mS/cm (approximate Na\textsuperscript{+} of 135 mEq/L). In the OCM protocol (Fresenius 4008 and later models), there is a single conductivity spike of 15.5 mS/cm for 60 to 90 seconds. Diascan employs a single conductivity step up of 1 mS/cm for 2 minutes.

Sodium ions and urea exhibit comparable diffusion characteristics across a dialyzer membrane. Their specific diffusion coefficient is almost identical at 37°C (Na\textsuperscript{+}: 1.94 × 10\textsuperscript{-5} cm\textsuperscript{2}/s, Urea: 2.20 × 10\textsuperscript{-5} cm\textsuperscript{2}/s).\textsuperscript{10} By indirect estimation of Na\textsuperscript{+} concentrations in the dialysate from the conductivity at the inlet and outlet of the dialyzer, it is possible to determine its diffusion profile and calculate its EID. Thus, EID of Na\textsuperscript{+} is used to calculate the “diffusibility” of urea through the membrane and the determination of the urea clearance.\textsuperscript{14} For measurement of Na\textsuperscript{+} EID, conductivity sensor cells are installed in the inlet and outlet lines that carry dialysate to and from the dialyzer. Conductivity cells have been in use for over four decades and have been found to be reliable.\textsuperscript{12} The performance parameters of these cells are governed by various international standards such as International Electrochemical Commission standards such as IEC-60601-2-16 which require performance within ± 5% of the calculated theoretical conductivity. For machines made by Fresenius the measured conductivity by the cell is required to be within ± 0.4 mS/cm of the measurement performed using a stand-alone conductivity meter. Fresenius machines require calibration of the conductivity cells every 6 months. Testing of the OLC cells is recommended twice a month and a conductivity difference of > 0.4 mS/cm between the two cells, when no patients is being dialyzed, is considered a failed test and requires recalibration of the conductivity cells. Other manufacturers may have different maintenance schedules and the user should consult the service manual of the devices in use. These conductivity cells measure the dialysate conductivity before it enters the dialyzer and after it exits as “spent” dialysate.\textsuperscript{15} The relative areas under the curves for the two recorded conductivity signals reflect the diffusion of Na\textsuperscript{+} ions across the dialyzer membrane. The dialysate conductivity continues to drop as it passes through the dialyzer due to diffusion of Na\textsuperscript{+} into the blood. A higher drop in the dialysate conductivity...
conductivity indicates a higher diffusion of Na\(^+\) to the blood across the dialyzer membrane and vice versa.\(^{13}\) Diffusion of Na\(^+\) from blood to the dialysate occurs when the dialysate Na\(^+\) concentration is lowered below the baseline during the second phase (OLC method only), increasing the dialysate conductivity at the dialyzer outlet compared to the inlet. \( K_{ecn} \) is calculated from the changes in the dialysate conductivity by using the equation:

\[
K_{ecn} = \left[1 - \left(\frac{C_{Di2} - C_{Di1}}{C_{Do2} - C_{Do1}}\right)\right] \times \left[\frac{Q_d + Q_f}{C_{Di1}}\right]
\]

where \( C_{Di2} \) and \( C_{Di1} \) refer to dialysate outlet conductivity during the conductivity step-up and the baseline, respectively. \( C_{Do2} \) and \( C_{Do1} \) refer to inlet conductivity during the conductivity step-up and the baseline, respectively. \( Q_d \) and \( Q_f \) refer to dialysate and ultrafiltration rates, respectively. \( K_{t/V} \) is calculated using \( K_{ecn} \times \frac{t}{V} \) equation. The value of \( V \) can be derived from anthropometric formulas such as Watson's and entered into the machine for this calculation. It is important to note that EID of Na\(^+\) is inferred indirectly from the conductivity clearance. Conductivity of the dialysate is determined by its ionic content which is comprised predominantly of Na\(^+\) and the associated anions. A strong linear correlation \((r = 0.997)\) exists between dialysate Na\(^+\) and its conductivity in the range of Na\(^+\) concentration between 120 and 160 mEq/L.\(^{14}\) The equation for the calculation of \( K_{ecn} \) above uses changes in the dialysate conductivity from the baseline during \( K_{ecn} \) measurement. When no Na\(^+\) is transferred to the blood side, the output difference \((C_{Do2} - C_{Do1})\) in the dialysate conductivity becomes equal to the input difference \((C_{Di2} - C_{Di1})\) and their ratio becomes 1. In this case \( K_{ecn} \) and the clearance become zero. Conversely, if all ions are transferred to the blood side, \((C_{Di2} - C_{Di1})\) becomes zero and \( K_{ecn} \) becomes equal to \( Q_d \) plus \( Q_f \). The validation data of this mathematically derived clearance calculations as compared to in vitro and in vivo urea-based clearance is presented in the next section.

Online Clearance Monitoring measurement protocol employs a single short-term dynamic conductivity pulse of 15.5 mS/cm and is depicted in Figure 1. Diascan employs a 1 mS/cm step up of conductivity for a period of 2 minutes. The mathematical underpinnings of estimating EID from a short-term dynamic conductivity pulse were provided in depth by Goldau et al.\(^{13}\) Various manufacturers use different default schedules of EID based clearance measurements, which can be changed by the user. In the machines made by Fresenius, the default is 6 measurements per treatment. The first measurement is performed once the patient has been on dialysis for 15 minutes and the last treatment occurs 15 minutes prior to the scheduled treatment termination. The remaining 4 measurements are performed at the time interval evenly split between these measurements.

**Precision of EID compared to urea-based methods**

Steil et al. demonstrated that the Na\(^+\) EID is directly proportional to urea clearance in vitro and in 6 patients on MHD with a correlation of 0.998 between blood side urea clearance and \( K_{ecn} \) in the in vitro experiments.\(^{11}\) Kuhlmann et al.\(^{15}\) compared the results with conventional urea clearance-based values in 20 MHD patients. Online Clearance data correlated very well with the conventional measurements of urea clearance corrected for recirculation (blood side: \( r = 0.87 \), dialysate side: \( r = 0.82 \), \( P < 0.001 \)). \( K_{t/V} \) correlated well with spKt/V\(_{urea} \) \((r = 0.940, P < 0.001)\), single pool variable volume kinetic model eKt/V\(_{urea} \) \((r = 0.982, P < 0.001)\), Daugirdas' formula \((r = 0.951, P < 0.001)\), and direct urea quantification from the spent dialysate \((r = 0.900, P < 0.001)\). The analytical error range was only \( \pm 5\% \) by OLC. In both of these studies, most values were within an error range of only \( \pm 5\% \) to \( \pm 6\% \). By applying a short-term single dynamic conductivity pulse, Goldau et al.\(^{13}\) reduced the error limit to below \( \pm 5\% \) and concluded that the short duration of the single conductivity pulse enables correction for the access and cardiopulmonary recirculation. Other investigators have also reported an excellent correlation between Na\(^+\) EID and urea clearance.\(^{16,17}\) The study by Lindsay et al.\(^{16}\) reported that the
disagreement between EID, measured by Diascan and blood side urea clearance increased at higher clearance values. They attributed this to the effect of cardiopulmonary recirculation on urea clearance. When urea clearance values were adjusted for cardiopulmonary recirculation, the difference between EID and effective urea clearance significantly decreased.

When using EID to calculate $K_t/V$, the method used to estimate $V$ can introduce variability in $K_t/V$ calculation. Anthropometric formulas such as Watson’s formula have been reported to overestimate $V$ and their use can underestimate the delivered $K_t/V$ compared to $spKt/V$ measured with urea kinetic modeling. This confounding was highlighted in two studies. In a study by Al Saran et al.,$^{19}$ EID-based measurements were compared with $spKt/V_{\text{urea}}$ in 118 measurements in 17 patients on MHD on Fresenius 4008S$^\text{TM}$ system. The investigators derived $V$ from Watson’s formula for TBW. The mean (±SD) $spKt/V_{\text{urea}}$ was 1.37 ± 0.09, and mean (±SD) $K_{\text{ecn}}/V$ was 1.02 ± 0.15 ($P = 0.000$). $K_{\text{ecn}}/V_{\text{urea}} \geq 1.2$ was achieved in all treatments while $K_{\text{ecn}}/V \geq 1.2$ was achieved in only 17.64% treatments. The correlation between $spKt/V_{\text{urea}}$ and $K_{\text{ecn}}/V$ was very poor ($R = 0.48$). In another study of 45 MHD sessions in 11 pediatric patients, Marsenic et al. compared 168 $K_t/V_{\text{urea}}$ measurements with OLC measurements using Fresenius 2008K machines. The investigators used 3 different methods to calculate $V$ for OLC $K_t/V$ calculations; Melillis and Cheek (MC), KDOQI recommended total body water nomogram (TBWN), and OLC-derived $V$. Assuming that $K_{\text{ecn}}$ equals or is very close to blood-based urea clearance $K$, the $K_{\text{ecn}}X_1 T/V$ formula was solved for OLC derived $V$. $K_{\text{ecn}}/V$ when using OLC derived $V$ were most accurate ($P = 0.42$ for difference from $K_{\text{ecn}}/V_{\text{urea}}$ with absolute error of 0.14 ± 0.12 (SD). When TBWN-derived $V$ was used, $K_{\text{ecn}}/V_{\text{urea}}$ was consistently underestimated by 0.32 ± 0.22 (SD) by $K_{\text{ecn}}/V$. MC-derived $V$ resulted in even greater underestimation of $spKt/V_{\text{urea}}$ and $K_{\text{ecn}}/V$ was not recommended by the investigators for use with $K_{\text{ecn}}/V$. This paper signifies the importance of $V$ when using EID-based methods for comparisons with modelled $K_t/V_{\text{urea}}$.

Use of EID in vascular access surveillance

Routine monitoring of arteriovenous grafts and native arteriovenous fistulas is recommended by the National Kidney Foundation Clinical Practice Guidelines.$^{27}$ Due to the expense and inconvenience of Doppler ultrasound or magnetic resonance imaging,$^{28,29}$ indirect access flow (AF) measurements using techniques such as ultrasound dilution (UD) are favored in outpatient dialysis facilities. Ultrasound dilution technique has been validated with the direct flow measurements by Doppler ultrasound.$^{30}$

Lacson et al.$^{22}$ compared AF rates using OLC with UD within first 90 minutes of a HD session in 50 adult patients with ESRD$^{27}$ and reported a correlation of $> 0.9$ ($P < 0.0001$) between the two methods. Bland-Altman analysis showed that the concordance between UD-AF and OLC-AF was tighter at AF rates less than 1000 mL/min. A sensitivity analysis that excluded OLC-AF rates greater than 1000 mL/min showed improvement in the correlation between OLC-AF and UD-AF to 0.95 ($P < 0.0001$). When low flow was categorized at $< 600$ mL/min, all patients who would have been referred for imaging because of low UD-AF results also would have been referred using OLC-AF results.

Another study compared UD-AF and OCM-AF in 32 patients undergoing Online Hemodiafiltration.$^{23}$ There was no significant difference in the AF between the two methods and the correlation between the two methods was 0.95 ($P < 0.01$). A Bland-Altman plot demonstrated a good agreement between these two methods as well. The authors concluded that the vascular AF rate by OCM was highly accurate, easy to perform, and economical. Lindsay et al.$^{24}$ and others$^{25,26}$ have also reported similar correlation and concordance between EID-AF and UD-AF.

In summary, EID-based methods of AF measurement are reasonable low-cost alternatives to UD-AF and direct AF measurements. The EID-AF values show a tighter
Table 1 Summary of studies of EID for measurement of dialysis dose and access flow

| Reference                  | Equipment used               | n Pts. | n Mnts. | Comparator method                  | Volume (V) | Corr (r) | P for (r) | P for difference |
|----------------------------|------------------------------|--------|---------|------------------------------------|------------|----------|-----------|------------------|
| **Precision**              |                              |        |         |                                    |            |          |           |                  |
| Steil et al.¹¹             | In vitro studies             | NA     | NP      | BUN clearance                      | NA         | 0.998    | NP        |                  |
|                            | In vivo studies (NP)         | 6      | 30      | BUN clearance                      | NA         | NP       | NP        |                  |
| Kuhlmann et al.¹⁵          | Fresenius 4008               | 20     | 118     | BUN clearance (blood side)         | NA         | 0.867    | <0.001    |                  |
|                            |                              |        |         | BUN clearance (Dialysate side)     | NA         | 0.82     | <0.001    |                  |
|                            |                              |        |         | spKt/V                              | 0.94       | <0.001   |           |                  |
|                            |                              |        |         | eKt/V                               | 0.982      | <0.001   |           |                  |
|                            |                              |        |         | Kt/V Daugirdas                      | 0.951      | <0.001   |           |                  |
|                            |                              |        |         | Kt/V (spent dialysate)              | 0.90       | <0.001   |           |                  |
| Goldau et al.¹³            | Fresenius 4008               | 10     | 45      | eKt/V                               | Modeled    | 0.96     | NP        |                  |
| Lindsay et al.¹⁶           | Integra (Gambro-Dasco)       | 8      | 175     | Urea clearance (blood side)         | NA         | 0.92     | <0.00001  |                  |
|                            |                              |        |         | Urea clearance (dialysate side)     | NA         | 0.917    | <0.00001  |                  |
| Al Saran et al.¹⁹          | Fresenius 4008S              | 17     | 136     | spKt/V                              | Watson     | 0.48     | 0.000⁴    | <0.001           |
| Marsenic et al.²⁰          | Fresenius 2008               | 11     | 168     | spKt/V                              | MC         | 0.37     | NP        | <0.001           |
|                            |                              |        |         |                                    | TBWN       | 0.36     | NP        | <0.001           |
|                            |                              |        |         |                                    | OLC        | 0.66     | NP        | 0.423           |
| **AV Access Blood Flow**   |                              |        |         |                                    |            |          |           |                  |
| Lacson et al.²²            | Fresenius 2008               | 50     | 49      | Ultrasound Dilution                | NA         | 0.93     | <0.0001   |                  |
| Tirarathanagul et al.²³    | Fresenius 4008               | 32     | 32      | Ultrasound Dilution                | NA         | 0.95     | <0.01     |                  |
| Lindsay et al.²⁴           | Integra (Gambro-Dasco)       | 15     | 92      | Ultrasound Dilution                | NA         | 0.91     | <0.001    | NS               |
| Whittier et al.²⁵          | Fresenius 2008K              | 48     | NP      | Ultrasound Dilution                | NA         | 0.9      | <0.001    | NS               |
| Huang et al.²⁶             | Fresenius 2008K              | 18     | NP      | Ultrasound Dilution                | NA         | >0.856   | <0.001    | > 0.17           |

*For difference between calculated Kt/Vtrue and Kcalc/V; Corr = correlation; Mnts = measurements performed; MC = Mellits-Cheek formula; NA = not applicable; NP = not provided; Pts = patients; TBWN = total body water nomogram recommended by KDOQI.
correlation with UD-AF method below the AF of 1000 mL/min, the correlation is not as tight for access flow rates of greater than 1000 mL/min. However, the number of patients with AF of greater than 1000 mL/min was rather small in these studies. Currently, EID-based AF measurements are not recommended if the AF rates are greater than 2000 mL/min.

**Advantages of EID-based clearance monitoring**

The EID-based methods determine clearance “online” during the entire treatment period at predefined or programmed intervals and can be used to detect adverse effects of reductions in the blood and/or dialysate flow rates or dialyzer clotting. Clinicians can implement appropriate interventions without having to wait for the monthly laboratory measurement of the dialysis dose. No blood draws are needed for these measurements.

**The risk of Na\(^+\) loading during EID measurements**

Changes in the serum Na\(^+\) concentration and the potential for salt loading have been raised as possible risks associated with EID measurements due to spiking of dialysate Na\(^+\) up to 155 mEq/L required for these measurements.

Gotch et al.\(^\text{31}\) studied the effects of OLC measurements on blood inlet Na\(^+\) concentration in ESRD patients on MHD to determine if there was any salt loading during OLC measurements. The clinical part of the study was performed in 21 patients with ESRD using Fresenius 2008H machines equipped with OLC system. The investigators studied changes in blood inlet Na\(^+\) concentration using both baseline/high as well as high/low protocols. For the high/low protocol the dialysate conductivity was increased to 15.5 mS/cm from the baseline of 14.0 mS/cm during the first half of the measurement, followed by reduction in the dialysate conductivity to 13.5 mS/cm during the second half of the OLC measurement.

The blood inlet Na\(^+\) concentration increased by 2.5 ± 0.4 mEq/L (Mean ± SE, n = 21) with the step function increase of dialysate inlet Na\(^+\) by approximately 15 mEq/L during the baseline/high protocol. A much smaller change of −0.6 ± 0.3 mEq/L (Mean ± SE, n = 19) was seen during the high/low protocol indicating that during the entire procedure of OLC measurement there was no change in blood inlet (serum) Na\(^+\) concentration when using high/low protocol. However, during the measurements which last 4 to 7 minutes, the serum Na\(^+\) concentration did go up by about 2.5 ± 0.4 mEq/L (Mean ± SE) in the first 2 to 3 minutes followed by return to the baseline during the subsequent 2 to 3 minutes. During the baseline/high profile there was a positive sodium flux into blood over the entire measurement interval. Thus, the authors concluded that over the entire high/low interval, net Na\(^+\) flux to blood is substantially less than observed during the baseline/high interval. However, in this study the investigators did not measure post-dialysis serum Na\(^+\) concentration or net Na\(^+\) balance.

Kuhlmann et al.\(^\text{15}\) evaluated the accuracy and safety of OLC monitoring in 20 patients with ESRD on MHD. Their OLC measurement protocol employed a dialysate conductivity variation of ± 10% above and below the standard conductivity for about 10 minutes each, 2 to 3 times per hemodialysis session for 10 consecutive treatments. This represented a change in the dialysate Na\(^+\) from 140.2 to 155 mEq/L and then down to 132.5 mEq/L during testing. Conductivity range on the dialysis machines did not dialysate Na\(^+\) below 132.5 mEq/L. The subjects were interviewed regarding symptoms such as thirst, muscle cramps, headache, and nausea and vomiting after every study dialysis session. Serum Na\(^+\) concentrations were measured at the start of each hemodialysis session and prior to and 8 minutes after the test procedure. Electrolyte balance, calculated by the area under the curve and dialysate flow, was used as a parameter of ionic shift balance. All parameters of fluid homeostasis were compared with the baseline level of the last 10 hemodialysis sessions prior to the study. No patient reported a change in thirst, muscle cramps, headache, or nausea and vomiting in comparison with the baseline. Serum Na\(^+\), body weight, respiratory and heart rates at rest, arterial pO\(_2\) and pCO\(_2\) at the start of a hemodialysis session and BP at the start and end of dialysis remained unchanged in comparison with the baseline. There was an increase in the Mean (±SD) serum Na\(^+\) concentration of 0.2 ± 1.5 mEq/L (p < 0.002) measured 8 minutes after the conductivity pulse which was consistent with a calculated Na\(^+\) shift into the patient of 1.53 ± 7.62 mEq (Mean ± SD) per OLC measurement. There was no difference in Mean (±SD) serum Na\(^+\) concentration measured at the start of hemodialysis sessions during the OLC measurement period of the study in comparison with the baseline values (138 ± 1.7 vs. 139 ± 1.7 mEq/L, p = ns). However, post dialysis serum Na\(^+\) concentrations were not measured in this study. Based on these data, the authors concluded that there may be a net gain of 1.53 mEq of Na\(^+\) by the patient for each OLC measurement. They also noted that the net gain of 1.53 mEq of Na\(^+\) was not likely to result in any adverse clinical effect. According to the authors, 11 mL of extra UF...
Table 2 Summary of the studies of effects of EID measurement on Na\(^+\) balance

| Reference          | Equipment       | n (Patients) | Method                                      | Δ Serum Na\(^+\) post measurement (mEq/L) | Δ Na\(^+\) Pre or Post HD | P          |
|--------------------|-----------------|--------------|---------------------------------------------|------------------------------------------|--------------------------|------------|
| Gotch et al.\(^{31}\) | Fresenius 2008H | 21           | “High/Low” Profile                          | −0.6 (0.3) (Mean ± SE)                    | NP                       | NP         |
|                    |                 | 19           | “Baseline/High” for 3 min                    | 2.5 (0.4) (Mean ± SE)                     | NP                       | NP         |
|                    | In vitro       | NA           | “High/Low” Profile                           | −2.0                                     | NP                       | NP         |
|                    |                 | NA           | “Baseline/High” for 3 min                    | +6.3                                     | NP                       | NP         |
| Kuhlman et al.\(^{15}\) | Fresenius 4008  | 20           | “High/Low” Profile for 10 min each           | 0.2 (1.5) (Mean ± SD)                     | NP                       | <0.0001    |
|                    |                 |              |                                              | 1.0 (1.7) (Mean ± SD)                     |                          | NS         |
|                    |                 |              |                                              |                                          |                          |            |
| Moret et al.\(^{32}\) | Diascan Gambro  | NP           | Single conductivity pulse of 1 mS/cm for 5 min (4 to 8 pulses/treatment) | NP                                      | NP                       |            |
|                    |                 | 200 HD sessions | Single conductivity pulse of 1 mS/cm for 5 min (1 pulse/treatment) | NP                                      | NP                       |            |
| Lindsay et al.\(^{24}\) | Diascan Gambro | 15           | Single conductivity pulse of 1 mS/cm for 4 min | Pre 137.2 (3.3) Post 139 (1.6) Mean ± SD |                          |            |

Note: All patients were dialyzed against a dialysate Na\(^+\) of 140 mEq/L which could not be excluded as the cause of Δ Na\(^+\); NP, not provided.
would be sufficient to offset this gain of $\text{Na}^+$. It is important to recognize that the duration of conductivity pulse employed during this study was much longer than currently in use (10 vs. 2–3 minutes).

Two studies evaluated salt loading during $\text{Na}^+$ EID measurements when using Diascan system. In a study by Moret et al.,\textsuperscript{32} the investigators evaluated ionic mass balance (IMB) and plasma conductivity in 200 isovolemic hemodialysis sessions in patients with ESRD who had zero interdialytic weight gain. A total of 137 HD sessions were performed with 4 to 8 conductivity pulses and 63 sessions with only one conductivity pulse. A positive IMB indicated $\text{Na}^+$ removal from the patient while a negative value indicated gain of $\text{Na}^+$ by the patient. The results showed a highly significant correlation between pre-dialysis plasma conductivity (representative of plasma $\text{Na}^+$ concentration) and IMB (Spearman rank $r_s = 0.902$, $P < 0.005$), indicating that patients with lower pre-dialysis $\text{Na}^+$ concentration had most net gain of $\text{Na}^+$ during HD and vice versa emphasizing the role of dialysate $\text{Na}^+$ in determining the net $\text{Na}^+$ balance during HD. There was no correlation between IMB and the number of conductivity pulses (Spearman rank $r_s = 0.02$, $P = 0.328$).

In the study by Lindsay et al.,\textsuperscript{24} the investigators evaluated $\text{Na}^+$ balance during EID measurements as part of their comparison of EID-AF with UD-AF as previously discussed. The study included 15 ESRD patients and 60 HD treatments. Prescribed dialysate $\text{Na}^+$ concentration was 140 mEq/L for all treatments and was held constant throughout the study. EID measurements were performed using Diascan. The protocol for EID measurements differed from OLC measurements in two important aspects; the conductivity step up was 1 mS/cm during the first measurement and 2 mS/cm during the second measurement each lasting 4 minutes (2 minutes with the bloodlines in normal position and 2 minutes with the bloodlines reversed) and the dialysate conductivity was never lowered below the prescribed dialysate conductivity. The mean (±SD) plasma $\text{Na}^+$ levels were $137.2 \pm 3.3$ mEq/L before dialysis and $139.0 \pm 1.6$ mEq/L postdialysis, which were significantly different ($P < 0.001$). In 13 of 15 patients, the $\text{Na}^+$ levels were obtained for each of the 4 dialysis treatments. For each patient, the average plasma sodium levels were calculated from these four pre-dialysis and postdialysis plasma $\text{Na}^+$ values. Paired $t$ test analysis of these data showed a small but statistically significant ($P < 0.01$) increment in plasma sodium over the course of dialysis. The investigators were not able to define the contribution of EID measurements to the rise in plasma $\text{Na}^+$ concentration because of the prescribed dialysate $\text{Na}^+$ of 140 mEq/L in these patients. However, it is consistent with the published literature\textsuperscript{33} that plasma $\text{Na}^+$ concentrations tend to rise during HD treatment if the prescribed dialysate $\text{Na}^+$ is greater that the predialysis plasma $\text{Na}^+$.

In summary, results from in vitro experiments, mathematical models, and clinical studies from independent groups did not find any evidence of clinically relevant salt loading during EID measurements. Table 2 provides a summary of the studies discussed in this section.

It is, however, important to acknowledge that none of these studies measured the effects of hemodialysis or EID of $\text{Na}^+$ measurements on nonosmotic retention of $\text{Na}^+$ in the skin and the interstitium. A recent study by Dahlmann et al.,\textsuperscript{12} in 20 HD patients used MRI-$\text{Na}^+$ to show that compared with age matched controls, the skin $\text{Na}^+$ content increased with increasing age and lower Vascular Endothelial Growth Factor C levels in patients on HD. Hemodialysis treatment led to a decrease in the muscle and skin $\text{Na}^+$ content. The investigators did not report whether EID-$\text{Na}^+$ measurements were performed during the study HD treatments. Sodium removal via UF accounted for most of the net negative $\text{Na}^+$ balance during HD.

SUMMARY AND CONCLUSION

Dialysis adequacy measured by online $\text{Na}^+$ EID is a valid and reliable technique with excellent correlation with blood urea-based measurements. Online clearance monitoring allows the quantification of the dialysis dose and appropriate prescription changes during a treatment to achieve the target dialysis dose. Clinicians can immediately assess the effectiveness of their interventions within the same dialysis treatment. All of this is accomplished without the need to draw any blood samples. The capability of this technique to measure vascular access flow can help clinicians screen for vascular access dysfunction. There has been some concern for potential salt loading during these measurements. However, the published data from mathematical models, in vitro experiments, and clinical studies shows no evidence of salt loading from any of the EID testing methods. Although, serum $\text{Na}^+$ concentration may rise transiently during these measurements, it is the prescribed dialysate $\text{Na}^+$ concentration and the ultrafiltration volume that determine the net $\text{Na}^+$ balance and the final postdialysis $\text{Na}^+$ concentration.

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