Low Dialysate [K⁺] Decreases Efficiency of Hemodialysis and Increases Urea Rebound

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Abstract. In a previous study, it was reported that hemodialysis with dialysate [K⁺] (KD) of 1.0 or 2.0 mmol/L caused an increase in BP shortly after completion of treatment due to arteriolar constriction. With this background, it was hypothesized that a low KD might decrease dialysis efficiency by a similar mechanism. To evaluate this hypothesis, paired observations of two consecutive 3-h treatments, with KD of 1.0 or 3.0 mmol/L, were performed in 14 stable end-stage renal disease patients. A KD of 1.0 mmol/L resulted in lower values for both urea reduction ratio and Kt/V evaluated at completion of dialysis and 1 h thereafter. Values at equilibrium were urea reduction ratio 42 ± 1% versus 47 ± 2% (P < 0.02), Kt/V 0.65 ± 0.03 versus 0.73 ± 0.03 (P < 0.02) for KD 1.0 or 3.0 mmol/L, respectively. The mechanisms responsible for the observed differences in dialysis efficiency were examined using a urea kinetics model that predicts urea sequestration caused by impaired blood flow to urea-rich tissues. For this purpose, urea rebound and its effect on Kt/V (by means of ∆Kt/V, calculated as equilibrated minus single pool value) with KD 1.0 and 3.0 mmol/L were assessed. Greater urea rebound, 12.8 ± 1.6% versus 8.6 ± 1.4% (P < 0.001), and larger ∆Kt/V, 0.12 ± 0.01 versus 0.10 ± 0.02 (P < 0.02), were observed with KD 1.0 mmol/L compared with 3.0 mmol/L. The theoretical model accurately predicted the ∆Kt/V observed with KD 1.0 mmol/L. It is concluded that a low KD decreases dialysis efficiency. This effect is likely caused by reduced blood perfusion to nonvisceral organs, largely skeletal muscle. Conversely, hemodialysis with KD 3.0 mmol/L facilitates tissue perfusion, minimizes urea trapping in poorly perfused areas, and improves the efficiency of this treatment modality.

Maintenance of potassium balance in patients with end-stage renal disease (ESRD) requires the removal of a portion of dietary potassium by the dialysis procedure. This goal is achieved using dialysate [K⁺] (KD) below 4.0 mmol/L, and lower KD values should result in greater potassium removal (1). Acute lowering of body content and serum potassium levels by hemodialysis might have hemodynamic effects mediated by changes in vascular tone (2,3). In fact, we have demonstrated previously that a rapid and/or large K⁺ removal during hemodialysis produces rebound hypertension that is likely mediated, at least in part, by an increase in the systemic vascular resistance (4). Such vascular changes could modify removal of urea and other solutes by hemodialysis. In fact, disequilibrium among body compartments during hemodialysis has been recognized for more than 30 yr (5,6). We hypothesize that dialysis-induced K⁺ losses might have deleterious effects on the circulation that can increase disequilibrium and negatively affect dialysis efficiency. Consequently, the aim of this study was to compare the effects of a relatively low dialysate [K⁺] of 1.0 mmol/L, and those of a relatively high KD of 3.0 mmol/L, on dialysis efficiency assessed by urea removal indices. If differences in dialysis efficiency were demonstrated, the underlying mechanisms would be investigated.

Materials and Methods

Studies were performed in male volunteers with ESRD after obtaining informed consent. All patients received chronic dialysis at the Veterans Affairs Medical Center in Houston, Texas. Protocols were approved by the Institutional Review Boards for Human Research of the Houston Veterans Affairs Medical Center and Baylor College of Medicine. Dialysis using 1.0 or 3.0 mmol/L dialysate [K⁺] were conducted during two sequential treatments. The KD used during the first treatment was randomly assigned. Patients were in their usual state of health, and the same access was used during each study treatment. During the two study treatments, the patient's usual 4-h hemodialysis was shortened to 3 h to accommodate the entire protocol within a 4-h time frame. Electrolytes and pre-, post-, and 1 h postdialysis blood urea nitrogen (BUN) were obtained for each treatment. All patients received dialysis three times weekly with Cobe Centralsystem 3 dialysis machines (Cobe Laboratories, Lakeview, CO), and their usual dialyzer and hemodialysis protocol were used during the treatments. None of the patients received treatments using high-flux dialyzers because this technique increases urea rebound and would confound analysis of the data (7,8). The dialysate contained (in mmol/L) 140 sodium, 1.0 or 3.0 potassium, 104 chloride, 30 bicarbonate, 0.74 magnesium, 1.5 calcium, and 200 mg % dextrose. Calibrated electronic scales were used to measure the patient's pre- and postdialysis weights.

Efficiency of hemodialysis with KD 1.0 and 3.0 mmol/L was
calculated as: weights were 79.4 ± 3.6 and 77.2 ± 3.5 kg, respectively, and determined by the urea reduction ratio (URR) and Kt/V.

**URR**

\[ \text{URR}_{\text{post}} = \frac{\text{BUN}_{\text{pre}} - \text{BUN}_{\text{post}}}{\text{BUN}_{\text{pre}}} \]  

**URR_{1\text{-hour-post}}**

\[ \text{URR}_{1\text{-hour-post}} = \frac{\text{BUN}_{\text{pre}} - \text{BUN}_{1\text{-hour-post}}}{\text{BUN}_{\text{pre}}} \]

\( \text{BUN}_{\text{pre}} \) was obtained at the start of hemodialysis, \( \text{BUN}_{\text{post}} \) was obtained immediately at completion of dialysis, and \( \text{BUN}_{1\text{-hour-post}} \) was obtained 1 h after completion of treatment when urea had equilibrated. The postdialysis BUN was drawn from the machine where it was reduced to 50 ml/min. Kt/V was calculated as:

\[ \text{Kt/V} = -\ln(R - 0.008t) + \frac{\text{UF}(4 - 3.5R)}{W}, \]

where \( R \) is the ratio of \( \text{BUN}_{\text{post}} \) or \( \text{BUN}_{1\text{-hour-post}} \) to \( \text{BUN}_{\text{pre}} \), \( t \) is length of hemodialysis treatment in hours, \( \text{UF} \) is the volume of ultrafiltration, and \( W \) is postdialysis weight in kilograms. This second-generation formula is accurate over a wide range of \( \text{Kt/V} \) values and accounts for urea lost during ultrafiltration.

The mechanisms responsible for differences in dialysis efficiency with \( KD \) 1.0 and 3.0 mmol/L were assessed using the urea kinetics model of Daugirdas and Schneditz, which predicts the degree of urea sequestration and resulting change in Kt/V due to urea rebound (\( \Delta \text{Kt/V} \)) caused by impaired blood flow to urea-rich tissues. Thus, the degree of urea sequestration can be estimated by comparing the measured with predicted \( \Delta \text{Kt/V} \). Measured \( \Delta \text{Kt/V} \) is the difference between \( \text{Kt/V} \) calculated using the postdialysis and equilibrated 1 h postdialysis BUN values. The predicted \( \Delta \text{Kt/V} \) values were obtained using the following formulas:

\[ \text{Predicted} \Delta \text{Kt/V} = -0.6 \times \frac{\text{Kt/V}}{t} + 0.03 \]

\[ \text{Predicted} \Delta \text{Kt/V} = -0.47 \times \frac{\text{Kt/V}}{t} + 0.02 \]

Equation 4 applies to patients dialyzed by an arteriovenous fistula or graft, and equation 5 when a venous catheter is used as dialysis access. Measured and predicted \( \Delta \text{Kt/V} \) were determined after hemodialysis treatments with \( KD \) of 1.0 and 3.0 mmol/L to assess the effects of potassium removal on tissue perfusion and urea disequilibrium. A measured \( \Delta \text{Kt/V} \) lower than predicted would be compatible with improved perfusion of urea-generating tissues, resulting in decreased urea sequestration and less rebound in BUN.

**Statistical Analysis**

Statistical evaluations were carried out by ANOVA for paired data. Results are reported as means ± SEM.

**Results**

Fourteen patients with ESRD, 44 to 80 yr old (mean 61.9 ± 3.2 yr), participated in the study. All patients except one were dialyzed by permanent arteriovenous access. In agreement with our previous study (4), dialysate \([K^+]\) did not correlate with fluid removal assessed by changes in body weight or BP measurements at the initiation and completion of dialysis. With \( KD \) 1.0 mmol/L, initial and final body weights were 79.8 ± 3.5 and 77.4 ± 3.6 kg, respectively, and volume of ultrafiltration was 2.4 ± 0.3 L. With \( KD \) 3.0 mmol/L, initial and final body weights were 79.4 ± 3.6 and 77.2 ± 3.5 kg, respectively, and volume of ultrafiltration was 2.2 ± 0.3 L. When dialysis was provided with \( KD \) 1.0 mmol/L, systolic BP levels at initiation and completion of dialysis were 143 ± 9 and 135 ± 9 mmHg, respectively, and corresponding diastolic BP readings were 82 ± 3 and 75 ± 4 mmHg. With \( KD \) 3.0 mmol/L, systolic BP levels at initiation and completion of dialysis were 142 ± 9 and 137 ± 9 mmHg, respectively, and corresponding diastolic BP readings were 77 ± 5 and 78 ± 3 mmHg.

Figure 1 illustrates the effect of treatment with each \( KD \) on serum potassium. Predialysis serum \([K^+]\) was not significantly different between study groups, and hemodialysis decreased serum \([K^+]\) regardless of \( KD \) \((P < 0.002)\). One hour postdialysis, serum \([K^+]\) rebounded from 3.3 ± 0.2 to 3.6 ± 0.2 mmol/L \((P < 0.03)\), and from 3.8 ± 0.1 to 4.0 ± 0.2 mmol/L \((P < 0.02)\), when \( KD \) was 1.0 and 3.0 mmol/L, respectively. The values for serum \([K^+]\) postdialysis, and 1 h postdialysis were both larger when \( KD \) was 3.0 mmol/L \((P < 0.004)\).

Data on efficiency of dialysis evaluated by URR and Kt/V are depicted in Figures 2 and 3, respectively. Patients’ dialysis treatments were shortened to 3 h to accommodate the entire protocol into a 4-h period. Consequently, the shortened dialysis treatments resulted in relatively low URR and Kt/V compared with standard values obtained after 4 h of treatment. Use of a 3.0 mmol/L dialysate \([K^+]\) resulted in a higher URR compared with \( KD \) 1.0 mmol/L. (Figure 2). The difference was statistically significant for \( \text{URR}_{1\text{-hour-post}} \): 42% ± 1 and 47% ± 2 for \( KD \) of 1.0 and 3.0 mmol/L, respectively \((P < 0.02)\). Assessment of dialysis efficiency by Kt/V yielded an analogous result, as shown in Figure 3. Kt/V was greatest immediately after dialysis.
reduced dialysis efficiency observed with KD respectively (P of 0.65 ± 0.03 and 0.73 ± 0.03 for KD of 1.0 and 3.0 mmol/L, respectively (P < 0.001). Yet “rebound 1.0” was significantly larger than “rebound 3.0” (P < 0.01). When calculated as a percentage of the fall in BUN during dialysis, urea rebound was 12.8% ± 1.6 versus 8.6% ± 1.4 for KD of 1.0 and 3.0 mmol/L, respectively (P < 0.001).

Figure 5 compares the changes in URR and Kt/V due to urea rebound, expressed as percent change. Use of KD 3.0 mmol/L resulted in a smaller difference between post- and 1 h postdialysis values of both URR and Kt/V. URR decreased 12.8 ± 1.6% during the 1 h after completion of hemodialysis for KD of 1.0 mmol/L, and 8.6 ± 1.4% with KD 3.0 mmol/L (P < 0.001). Analogously, Kt/V measured 1 h postdialysis was 16 ± 1.8% lower when KD was 1.0 mmol/L, and 11.5 ± 1.9% with KD of 3.0 mmol/L (P < 0.001). In addition, Figure 5 demonstrates that the percentage change in Kt/V due to urea rebound was greater than that observed for URR, regardless of KD (P < 0.001). This indicates that the second-generation Kt/V formula is more sensitive to urea rebound than URR, and the effects of urea rebound were more pronounced when dialysis efficiency was assessed by Kt/V.

Figure 6 depicts measured ΔKt/V in our patients and predicted ΔKt/V when urea trapping caused by low blood perfusion to the urea-rich compartment has occurred during dialysis. Comparison between the actual and predicted ΔKt/V will give insight into whether KD modifies regional blood flow and tissue perfusion during dialysis, altering the efficiency of this treatment. As shown in Figure 6, measured and predicted ΔKt/V were almost identical with KD 1.0 mmol/L, supporting the hypothesis of underperfusion during dialysis with the low KD. In contrast, for KD of 3.0 mmol/L, actual ΔKt/V is significantly less than the predicted value (−0.0996 ± 0.0184 postdialysis, and was less 1 h later due to urea rebound (P < 0.001). Treatments with KD of 3.0 mmol/L resulted in higher Kt/V compared with KD of 1.0 mmol/L. The difference was statistically significant for Kt/V at 1 h postdialysis, with values of 0.65 ± 0.03 and 0.73 ± 0.03 for KD of 1.0 and 3.0 mmol/L, respectively (P < 0.02).

Data obtained to examine the underlying mechanisms for the reduced dialysis efficiency observed with KD 1.0 mmol/L are depicted in Figures 4 through 6. Urea rebound is shown in Figure 4, which presents BUN levels pre-, post-, and 1 h postdialysis. Significant urea rebound was observed in both groups (P < 0.001). Yet “rebound 1.0” was significantly larger than “rebound 3.0” (P < 0.01). When calculated as a percentage of the fall in BUN during dialysis, urea rebound was 12.8% ± 1.6 versus 8.6% ± 1.4 for KD of 1.0 and 3.0 mmol/L, respectively (P < 0.001).

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Figure 5. Low KD increased the difference between urea kinetics calculations made with BUN obtained immediately post, or 1 h after dialysis. KD of 3.0 mmol/L minimized urea rebound and the variation in calculated dialysis efficiency whether assessed by URR or Kt/V. Urea rebound had a greater effect on Kt/V compared with URR regardless of KD. *P < 0.001 compared with dialysate [K+] of 1.0; #P < 0.001 compared with URR.

Figure 6. KD of 3.0 mmol/L caused change in Kt/V due to urea rebound (ΔKt/V) to be less than predicted. The predicted ΔKt/V indicates urea trapping due to underperfusion of urea-rich tissues during hemodialysis (10). Measured ΔKt/V less than the predicted value is compatible with improved perfusion of urea-rich tissue beds, resulting in less urea rebound postdialysis.

versus −0.1344 ± 0.0080, P < 0.02). Consequently, urea trapping caused by reduced blood flow to tissue beds decreased with the use of higher concentrations of potassium in the dialysate.

Discussion
This study describes a heretofore unrecognized effect of dialysate [K+] on urea clearance during hemodialysis. Treatments with a low dialysate [K+] of 1.0 mmol/L decreased dialysis efficiency in comparison with hemodialysis treatments using a relatively high KD of 3.0 mmol/L. The effects of a low KD appear to be mediated by a decrease in body fluid [K+] (Figure 1) that induces a transient reduction in blood flow to urea-rich tissues, as discussed in greater detail below. Such vascular effects elicited by K+ removal from body fluids should not come as a surprise. In fact, data from our laboratory (2) and others (3) have documented constrictor effects on the circulation by a low extracellular [K+], and vasodilatory effects associated with potassium loading.

The current investigation was conceived after our previous observations that an acute decrease in serum potassium due to hemodialysis produces “rebound hypertension” that becomes apparent after completion of treatment (4). Hypokalemic “rebound hypertension” is likely mediated, at least in part, by constriction of arterioles in the systemic circulation. It was our hypothesis that the arteriolar constriction responsible for the postdialysis “rebound hypertension” would likely be present during the dialysis treatment period, and might interfere with dialysis efficiency. Since the goal of the current investigation was an evaluation of the effects of KD on urea removal indices, we did not perform postdialysis assessment of BP levels.

The present study demonstrates that dialysis efficiency evaluated by means of URR and Kt/V decreases significantly with the use of KD 1.0 mmol/L compared with 3.0 mmol/L (Figures 2 and 3). We selected 1.0 mmol/L for the low KD rather than the more commonly used 2.0 mmol/L to make possible differences more evident. However, we believe that the reduction in dialysis efficiency with a lower KD is likely present with intermediate [K+] (i.e., 2.0 mmol/L), since there is no evidence for the existence of a threshold value for the vascular effects of potassium. In addition, we performed paired observations to remove confounding variables that might obfuscate the results of this investigation.

To examine the underlying mechanisms for the reduced dialysis efficiency observed with KD 1.0 mmol/L, we used the theoretical model and equations described by Daugirdas and Schneditz (9–11). These investigators critically evaluated the two current views of the site of urea sequestration (i.e., the intracellular space versus low blood flow to body compartments with high urea content) by means of theoretical modeling and observational data. Their regional blood flow model accurately predicted overestimation of hemodialysis dose. Our use of the equations derived from this model allowed us to calculate the predicted ΔKt/V with KD 1.0 and 3.0 mmol/L, depicted in Figure 6. A remarkable similarity between the measured ΔKt/V (obtained as the difference between equilibrated and immediately postdialysis Kt/V values) and the predicted ΔKt/V (based on the existence of an underperfused urea-rich body compartment) was found with KD 1.0 mmol/L. On the other hand, a marked discrepancy was found between measured ΔKt/V and predicted ΔKt/V with KD 3.0 mmol/L. The discrepancy observed with KD 3.0 mmol/L in association with a significantly smaller measured ΔKt/V than the predicted value indicated decreased urea trapping during dialysis with high KD. Conversely, the similarity of predicted and measured ΔKt/V with KD 1.0 mmol/L is interpreted as indicative of a large sequestered pool of urea in underperfused body tissues.

We propose that an acute decrease in extracellular [K+] during hemodialysis with low KD produces constriction in several vascular beds, including the extremities. Because mus-
cles, bones, and skin contain approximately 80% of the volume of distribution of urea but may receive only 20% of cardiac output in the course of hemodialysis with low KD, sequestration of a sizable amount of urea might occur (10). Consequently, dialysis efficiency decreases, a large postdialysis urea rebound occurs (Figure 4), and routine urea kinetic calculations might be inaccurate (Figure 5) (12–14). Some urea rebound remains, however, even with the use of the greater KD. We propose that even with KD 3.0 mmol/L, a small degree of urea trapping is still present in tissue beds (9–11,15–17). This explanation is in concert with our view that rapid and/or excessive removal of potassium during hemodialysis causes underperfusion of urea-rich vascular beds.

In summary, this study demonstrates that hemodialysis with a KD of 1.0 mmol/L decreases dialysis efficiency. Furthermore, low KD might lead to overestimation of dialysis dosage because of augmented urea rebound. We propose that these effects are mediated by decreased blood flow to urea-rich tissues secondary to vasoconstriction. Diminished dialysis efficiency caused by aggressive potassium removal might significantly contribute to the morbidity and mortality of patients with ESRD.

Acknowledgments

We thank the dialysis nurses and technicians at the Veterans Affairs Medical Center (Houston, TX) for their help in setting up the specific dialysis treatments, and obtaining the blood samples.

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