Multicenter Clinical Validation of an On-Line Monitor of Dialysis Adequacy1,2


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ABSTRACT

Quantification of hemodialysis by measuring changes in blood solute concentration requires careful timing when taking the postdialysis blood sample to avoid errors from postdialysis rebound and from recirculation of blood through the access device. It also requires complex mathematical interpretation to account for solute disequilibrium in the patient. To circumvent these problems, hemodialysis can be quantified and its adequacy assessed by direct measurement of the urea removed in the dialysate. Because total dialysate collection is impractical, an automated method was developed for measuring dialysate urea-nitrogen concentrations at frequent intervals during treatment. A multicenter clinical trial of the dialysate monitoring device, the Biostat® 1000 (Baxter Healthcare Corporation, McGaw Park, IL) was conducted to validate the measurements of urea removed, the delivered dialysis dose (Kt/V), and net protein catabolism (PCR). The results were compared with a total dialysate collection in each patient. Dur-

1 Received April 10, 1995. Accepted November 29, 1995.
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1046-6673/95/$0.00/0
Journal of the American Society of Nephrology
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ing 29 dialyses in 29 patients from three centers, the paired analysis of urea removed, as estimated by the dialysate monitor compared with the total dialysate measurements, showed no significant difference (14.7 ± 4.7 g versus 14.8 ± 5.1 g). Similarly, measurements of Kt/V and PCR showed no significant difference (1.30 ± 0.18 versus 1.28 ± 0.19, respectively, for Kt/V and 42.3 ± 15.7 g/day versus 52.2 ± 17.4 g/day for PCR). When blood-side measurements during the same dialyses were analyzed with a single-compartment, variable-volume model of urea kinetics, Kt/V was consistently overestimated (1.49 ± 0.29/dialysis, P < 0.001), most likely because of failure to consider urea disequilibrium. Because urea disequilibrium is difficult to quantify during each treatment, dialysate measurements have obvious advantages. The dialysate monitor eliminated errors from dialysate bacterial contamination, simplified dialysate measurements, and proved to be a reliable method for quantifying and assuring dialysis adequacy.

Key Words: Urea kinetics, adequacy, dialysate Kt/V

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nderdelivery of dialysis is usually asymptomatic initially, but cumulative effects cause significant patient morbidity over a period of time. Moreover, the effects of underdialysis are not easily or quickly corrected. In the initial National Cooperative Dialysis Study, patients in the short-time, low time averaged BUN (TAC) group (Group 4) continued to show a proportionately higher rate of mortality in the 12 months of follow-up after they were removed from the study and their therapy was increased (1). Regular use of urea kinetic modeling as part of a total-quality management system can help prevent this source of therapy failure.

Unfortunately, despite the availability of information, software, and experience, urea modeling remains underutilized (2,3). Quantitation of hemodialysis by traditional blood-side modeling of predialysis and postdialysis urea nitrogen concentrations is subject to error because of: (1) disequilibrium in urea distribution that occurs within the patient as a consequence of the dialysis; (2) recirculation of dialyzed blood to the dialyzer; and (3) cardiopulmonary recirculation. These states of urea disequilibrium distort the simple first-order relationships between blood levels and the amount of urea removed, causing errors in the traditional single-compartment analysis of urea kinetics within the patient. More accurate measurements require multiple blood samples and complex mathematical analyses to assess the quantity of dialysis deliv-
Patients were allowed to participate in the study if they were 50 years of age, had a history of renal failure, and were on hemodialysis. Two of these centers were within the United States (Regional Kidney Disease Program, Minneapolis, MN; University of California, Davis, CA) and one was Canadian (Victoria General Hospital, Halifax, Nova Scotia). Patients were allowed to participate in the study if they were clinically stable, hemodialyzed three times weekly, able to give informed consent, and had not been hospitalized within the previous 30 days. Patients known to have circulating antibodies to hepatitis B surface antigen or to human immunodeficiency virus (HIV) were excluded a priori. The primary causes of renal failure were randomly distributed, with the majority resulting from glomerulonephritis (18.7%), hypertension (21.8%), diabetes (15.6%), and polycystic kidney disease (15.6%).

Urea Monitor

The dialysate urea monitor (Biostar® 1000, Baxter Healthcare Corporation, McGaw Park, IL) connects to the effluent dialysate line of the dialysis delivery system and periodically aspirates samples of dialysate. The concentration of urea in the sample is then measured by bringing it in contact with a urease-impregnated membrane and measuring the resulting ammonium ion with an ion-specific electrode. This results in a double-exponential concentration-time profile from which urea removal, whole body Kt/V, and other associated parameters such as PCR can be derived. Unlike current blood sampling methods, these parameters are available immediately at the end of treatment and with a high degree of accuracy because of the frequent sampling. Projected estimates of these parameters are printed after 90 min of treatment so that problems can be detected before the end of the session.

Study Design

Dialysate urea concentrations were monitored on-line during each dialysis in each patient for 1 wk, for a total of three treatments per patient (94 actual treatments). The monitor was programmed to take dialysate samples every 5 min for the first half hour of the treatment and every 10 min thereafter. An equilibration sample was also taken before each monitored treatment, when possible. This was accomplished either by placing the dialysis machine into bypass or by stopping the dialysate flow while continuing ultrafiltration for 5 min with the blood pump running, and then allowing the dialysate monitor to sample the resulting equilibrated dialysate. The urea concentration in this dialysate, when it is fully equilibrated, is equal to the plasma water concentration of the blood. Plasma water was assumed to be 93% of plasma volume. For some of the dialysis machines used in the study (I.E., Monitral®; Hospal Inc., Lyon, France), an equilibration sample could not be obtained because of the volume of the dialysate loop (1 L) and the fact that this dialysate continues to circulate during bypass. Under these circumstances, Kt/V and PCR could still be determined, but K and V could not be separated.

Blood samples were also obtained during the second study week, as shown in Table 1, and one additional sample was taken immediately before the first treatment of the following week. Predialysis samples (C0) were taken before the patient was connected to the dialyzer; postdialysis samples (Cp) were taken within 30 s after shutting off the blood pump and flushing dead space from the fistula line. An additional sample (Cf) was taken 30 min after treatment on the second session of the week to measure the rebound in BUN. All blood samples were centrifuged immediately after treatment and the serum was separated for BUN measurements by the clinical laboratory.

The total effluent dialysate was collected during the second treatment as shown in Table 1. Because the contamination of bicarbonate dialysate is well documented (13) and can result in an underestimation of urea removed, samples were filtered
through a 0.22 µ filter before being placed in sterile plastic tubes. This necessity of dialysate decontamination was underscored by the poor results obtained during an earlier study that utilized the same methodology (see "Results").

The parameters V, G, Kt/V, and PCR were also calculated by using a variable-volume single-pool model (VVSP) of blood urea-nitrogen concentrations (UKM) according to the method of Gotch and Sargent (14). Access recirculation was measured during the week before the study by using a three-sample stop-flow technique (15). Those patients with greater than 15% recirculation were screened from the VVSP calculations (one patient). The dialyzer clearance was measured on the dialysate side (16) by using dialysate and blood samples taken at 30 and 60 min. Dialysate flow was measured by timing a collection of dialysate into a 2-L volumetric flask. The ultrafiltration rate was calculated as the patient's predialysis weight minus the postdialysis weight divided by the actual time of dialysis. Residual urea clearance was calculated from the measurement of urea nitrogen in urine collected by the patient over a 48-h period during the second week of the study.

The solute removal index (SRI) was calculated by the dialysate urea monitor and reference dialysate method. This is defined as the net removal \( R - G \cdot T_d \) normalized to the predialysis body content of urea. \( G \) is the urea generated during dialysis. The urea reduction ratio is similar to the SRI but neglects the effects of urea generation, ultrafiltration, and urea disequilibrium during dialysis.

**Reference Dialysate Method**

The direct-dialysate quantification method of Malchesky et al. and Ellis et al. (6,7) was modified to reflect volume changes that resulted from ultrafiltration and the two-pool nature of urea removal as outlined below. This was used as the primary reference method (mDDQ). The total amount of urea removed in the dialysate was measured by collecting all dialysate during the second treatment of the study week (Table 1). The effluent dialysate was collected in hourly aliquots to take advantage of the increased accuracy and precision possible when measuring the higher solute concentrations early in dialysis. The aliquots were mixed and weighed and the samples were analyzed for urea nitrogen. Removal \( R \) was calculated as the aggregate of the hourly collections. To limit contamination, samples were filtered through a 0.22-µ sterile filter into a sterile plastic container and were refrigerated soon after collection.

From an intradialytic mass balance using the blood and dialysate removal data, the volume of urea distribution after dialysis \( (V\text{ in mL}) \) is calculated according to:

\[
V = \frac{R - G(T_d + 30) - UF(C_{\text{bo}}/0.93)}{(C_{\text{bo}}/0.93) - C_p/0.93)}
\]

where \( T_d \) is the duration of the dialysis treatment in minutes, \( G \) is the generation rate of urea nitrogen in mg/min, \( UF \) is the number of mL removed during the treatment, and 30 is the rebound duration. The 0.93 factor is used to convert serum to plasma water concentrations. \( C_{\text{bo}} \) and \( C_p \) are the predialysis BUN and the BUN following the 30-min rebound in mg/mL. The generation rate is simultaneously calculated from consideration of interdialytic mass balance according to:

\[
G = \frac{V(C_{\text{bo}}/0.93 - C_p/0.93) + WTG(C_{\text{bo}}/0.93) + C_0V_U}{T_d - 30}
\]

where \( WTG \) is the interdialytic weight gain in grams, \( T_d \) is the interdialytic interval in min, \( C_0 \) is the urine concentration in mg/mL, and \( V_U \) is the urine volume in mL. \( C_{\text{bo}} \) is the 30-min rebound concentration from the previous day (Treatment 1 of the week). Because a 30-min rebound sample was obtained only during Treatment 2, \( C_{\text{bo}} \) was calculated from the immediate postdialysis concentration with a correction for rebound, assuming that the patient had a similar degree of rebound for both Treatment Days 1 and 2.

Equations 1 and 2 were solved iteratively until \( V \) and \( G \) converged within 1%. Whole body clearance \( (K\text{ in mL/min}) \) was calculated as removal divided by the product of treatment duration and log mean concentration:

\[
K = \frac{R \ln(C_{\text{bo}}/C_p)}{T_d(C_{\text{bo}} - C_p)/0.93}
\]

\[ (3) \]

The two-pool \( Kt/V \) was then calculated by using \( T_d \), \( K \) from Equation 3, and \( V \) from Equation 1. PCR (g/day) was calculated from the Borah et al. (17) equation as 9.35G + 0.294V. This may be normalized to body weight (PCRn in g/kg per day) by dividing PCR by \( V/0.58 \). The latter normalization factor is a convention from Gotch and Sargent (14).

**TABLE 1. Schedule of sampling during study**

<table>
<thead>
<tr>
<th>Week</th>
<th>Blood</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialysis BUN</td>
<td>30-min BUN</td>
<td>Predialysis BUN</td>
<td>30-min postdialysis BUN</td>
<td></td>
</tr>
<tr>
<td>Postdialysis BUN</td>
<td>60-min BUN</td>
<td>Postdialysis BUN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysate</td>
<td>30-min urea nitrogen</td>
<td>60-min urea nitrogen</td>
<td>Hourly total volume</td>
<td>Hourly urea nitrogen</td>
</tr>
</tbody>
</table>
Statistical Methods

The urea monitor has the capability of evaluating the quality of the sample data and indicating which monitoring sessions need to be repeated. These sessions are described by the term "fit error" and were excluded from the statistical analysis. Fit errors result when more than four dialysate samples are rejected by the monitor's internal quality-control software. These are usually a consequence of substantial changes in operating parameters during the course of treatment, such as frequent adjustment of blood flow, machine alarms, or access clotting. Results are still reported when there is a fit error and are often valid, on the basis of past experience with the patient, but they should be interpreted with extra caution. The eight treatments (three occurring during the comparison treatment) that had fit errors were excluded from both the accuracy and reproducibility analyses as required by the protocol. Incomplete treatments were defined as those treatments in which the monitored duration deviated from the prescription duration by more than 30 min. Because treatment duration affects Kt/V, the one incomplete treatment was excluded from the reproducibility analysis but not the accuracy analysis.

When the predialysis equilibration procedure is performed incorrectly, a lower-than-normal equilibration concentration can result. This in turn can result in unphysiological urea distribution volume to patient weight ratios (V/W). An outlier analysis was conducted on an earlier data set by using a standard statistical technique (the five sigma method) and prediction intervals on V/W were computed at the confidence level of 99%. These limits are currently part of the device's internal quality-control software so that outcomes dependent on the predialysis equilibration sample (equilibrated DUN, V, K, Pcrn, and SRI) are not reported when the V/W limits are exceeded (i.e., V/W > 68.6% or V/W < 22.8%). As a result, the above outcomes were excluded for the two treatments in which V/W limits were exceeded. Also, in 21 instances, the predialysis equilibration sample was not taken, as per protocol, because of the type of delivery system (Hospal® and in one instance, protocol was accidentally violated by a shortened equilibration time. The equilibration dependent outcomes in these cases (eight during the comparison treatment) that had fit errors were therefore excluded from analysis.

The concordance correlation coefficient (CC), a measure of the degree to which pairs of observations fall on the line of identity (18), was used to compare the dialysate concentration monitor (DCM) and the mDDQ results. The CC is equal to the product of the Pearson correlation coefficient (the precision factor) and an accuracy factor that indicates systematic bias. CC values of 1 indicate that the pairs of observations are identical, whereas CC values close to 0 indicate no relationship. The parameters that were compared included predialysis urea concentration, Kt/V, Pcrn, PCR, urea removal (R), volume of urea distribution (V), whole-body urea clearance (K), and solute-removal index (SRI) (11).

The reproducibility of the outcome measures was calculated as the pooled-within-patient coefficient of variation (CV) for the three treatment sessions, subject to the exclusions described above. More precisely, this is the square root of the weighted average of the individual variances (19) divided by the mean. Reproducibility could not be calculated for the reference method because only a single measurement per patient was performed.

Results

Figure 1 shows the urea removal determined by DCM compared with the urea in the total dialysate collection for an earlier study at the same three centers and two additional ones (University of California at Los Angeles, Los Angeles, CA; and Brigham and Women's Hospital, Boston, MA). The large dispersion of the data and the poor concordance between the two methods was unexpected because the area under the concentration-time curve multiplied by dialysate flow should coincide with direct measurement of urea in the total dialysate. Urea distribution volume showed even less concordance and, when measured by the total collection method, appeared to be much lower than expected (32% of body weight). On the basis of
TABLE 3. Reproducibility of outcome measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DCM CV Within Patients</th>
<th>VVSP CV Within Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>11.8%</td>
<td>N/A</td>
</tr>
<tr>
<td>Kt/V</td>
<td>6.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>PCR</td>
<td>5.6%</td>
<td>6.0%</td>
</tr>
<tr>
<td>PCRn</td>
<td>9.5%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Volume</td>
<td>8.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td>SRI</td>
<td>12.7%</td>
<td>N/A</td>
</tr>
<tr>
<td>SRI</td>
<td>12.8%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Bold numbers are for the 65 matched runs (complete sets of 3 treatments on each of 22 patients). N = 23 patients (69 treatments). N/A = not available.

TABLE 2. Outcome parameters by mDDQ and DCM methods

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>DCMa</th>
<th>mDDQa</th>
<th>CCb</th>
<th>Lower Limitc</th>
<th>Precision (p)</th>
<th>Accuracy Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal (g)</td>
<td>29</td>
<td>14.7 ± 4.7</td>
<td>14.8 ± 5.1</td>
<td>0.97</td>
<td>0.94</td>
<td>0.97</td>
<td>1.00 (0.996)</td>
</tr>
<tr>
<td>Kt/V (per dialysis)</td>
<td>29</td>
<td>1.30 ± 0.18</td>
<td>1.28 ± 0.19</td>
<td>0.81</td>
<td>0.67</td>
<td>0.81</td>
<td>1.00 (0.995)</td>
</tr>
<tr>
<td>PCRn (g/kg per day)</td>
<td>23</td>
<td>1.03 ± 0.27</td>
<td>1.00 ± 0.28</td>
<td>0.86</td>
<td>0.72</td>
<td>0.86</td>
<td>0.99</td>
</tr>
<tr>
<td>Volume (L)</td>
<td>22</td>
<td>30.9 ± 7.2</td>
<td>31.9 ± 8.7</td>
<td>0.93</td>
<td>0.87</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>Clearance (mL/min)</td>
<td>22</td>
<td>225 ± 27</td>
<td>229 ± 36</td>
<td>0.89</td>
<td>0.81</td>
<td>0.94</td>
<td>0.95 (0.999)</td>
</tr>
<tr>
<td>PCR (g/day)</td>
<td>29</td>
<td>52.3 ± 15.7</td>
<td>52.2 ± 17.4</td>
<td>0.95</td>
<td>0.91</td>
<td>0.96</td>
<td>1.00 (0.995)</td>
</tr>
<tr>
<td>Predialysis equilibrated UN (mg/dL)</td>
<td>72</td>
<td>61.1 ± 6.1</td>
<td>61.8 ± 7.8</td>
<td>0.97</td>
<td>0.96</td>
<td>0.97</td>
<td>1.00 (0.998)</td>
</tr>
<tr>
<td>SRI</td>
<td>23</td>
<td>0.677 ± 0.042</td>
<td>0.685 ± 0.050</td>
<td>0.80</td>
<td>0.67</td>
<td>0.82</td>
<td>0.97</td>
</tr>
</tbody>
</table>

a DCM and mDDQ parameters are the mean ± SD.
b CC is the concordance coefficient between methods and is the product of precision (p) and accuracy (C) factors.
c Lower limit is the 95% confidence limit on CC that indicates the degree of uncertainty introduced by the finite sample size.
d PCR and PCRn include the contribution of residual renal function.
modified direct-dialysate quantification method. The accuracy factor was between 0.95 and 1.0 for all of the outcome parameters, indicating very little systematic bias between the two methods. The precision factor ranged from 0.81 to 0.97. A comparatively low precision factor might be caused by the low reproducibility of either method. The larger standard deviation observed for most of the parameters derived from the mDDQ method suggests that the DCM method is more reproducible but this cannot be verified without repeated measurements. Concordance coefficients were higher than 0.80, for all eight of the outcome parameters. The 0.80 value is an acceptable limit for clinical measurements. The most precise measurements and those with the highest CC are those directly measured, such as urea removal (Figure 2). Derived measurements such as \( Kt/V \) (Figure 3) or PCRN (Figure 4) are somewhat less precise but still acceptable. Indeed, despite the seeming dispersion of these latter parameters, a paired \( t \) test showed no significant difference between the means (\( P = 0.48 \) and \( P = 0.25 \), respectively) suggesting that the DCM methodology is indistinguishable from the mDDQ.

It should be pointed out that despite its successful use here, the mDDQ method is, in practice, quite cumbersome. The handling of large amounts of dialysate and the care that must be taken to ensure that the containers are cleaned between use and the dialysate samples are decontaminated and stored in a sterile fashion make the method unattractive for routine practice. In addition, to calculate the true \( V \) and an accurate whole-body \( Kt/V \), the patient needs to remain in the unit an extra 30 min or longer so that a post-rebound blood sample may be obtained. This presents obvious logistical problems, as well as an inconvenience to the patient. Finally, the clinical laboratory must have experience in measuring dialysate samples by using aqueous standards in the range expected for effluent dialysate, and must be aware of any assay bias. The dialysate matrix is different than the serum or urine matrix so that submitting aqueous standards is a prudent measure to ensure data integrity. These difficulties with mDDQ do not apply to the dialysate monitor, which is optimized for dialysate measurement and does not require a postdialysis rebound sample.

The mDDQ as presented here assumes that rebound is complete at 30 min after dialysis. Pedrnì et al. (21) and, more recently, the investigators of the HEMO Pre-Pilot Study (22) have shown that while substantially complete, some rebound may continue to occur after 30 min, depending on the patient's intercompartmental transfer coefficient or variations in regional blood flow (23,24). Pedrìnì et al. took blood samples every 5 min after dialysis for 1 h and fit this data to a \( 1-e^{-n} \) function. They found that the average rebound was 99% complete at 48 min and 94.3% complete at 30 min if the generation rate is neglected. This implies that the 30-min rebound sample is 99/94.3 = 4.9% too low. The HEMO study group determined on the basis of their data set, which was more extensive than that of Pedrìnì et al., that this ratio should be 3.9%. Because rebound is patient specific, however, rather than utilizing a global empirical correction, we followed the lead of the HEMO kinetic
modeling pilot study analysis group (T. Greene, HEMO Pilot Study KM Analyses, personal communication.) and computed the equilibrated post-dialysis concentration with an "adjusted 3 point exact solution method." This involved doing a numerical solution of the two-pool variable extracellular volume model adjusted for cardiopulmonary recirculation and fitting this solution to measured before, after, and 30 min-after BUN values with appropriate choices for the two transfer coefficients (Kc and Kc) so as to minimize the sum of the squares of the differences between the measured and predicted concentrations. Estimates of generation rate and volume were taken from a single-pool variable volume model using the method of Depner (25). The equilibrated concentration was then computed from the postdialysis intracellular and extracellular concentrations and volumes.

Figure 5 shows the equilibrated concentration versus the 30-min post-dialysis concentration (with the effect of generation subtracted) for the patients of the study group. The three fit errors were excluded, as noted previously, for consistency with earlier results, although their inclusion neither changes the correlation nor concordance coefficients. One data point did have to be excluded because of "negative rebound" (i.e., the concentration at 30 min after dialysis was reported to be less than the concentration immediately after dialysis). Data points such as this do not fit the two-pool model, which assumes a positive rebound, and are almost always a result of laboratory or procedural error. This illustrates the types of problems that can arise when the calculation of a kinetic parameter is dependent on a single sample point. The extremely good concordance (CC = 0.996) between the equilibrated and generation corrected 30-min postdialysis sample suggests, at least in this data set, that the two are equivalent and the measured 30-min value can be used in lieu of the former in the mDDQ.

The solute removal index that is calculated from removal, predialysis DUN, and V, has a concordance with the mDDQ similar to that for Kt/V (CC = 0.80). Unlike Kt/V, which needs to be scaled depending on dialysis modality or intermittency of the therapy, SRI yields the same weekly measurement of therapy independent of how it is administered, and without invoking theories such as the peak concentration hypothesis (26). SRI also has an intuitive appeal because it is based on a quantity that is directly measured, such as removal, rather than being derived from predialysis and postdialysis blood concentrations that are subject to a great many extrinsic influences, such as distribution volume, access recirculation, cardiopulmonary recirculation, etc. This brings the focus of adequacy back to the patient (i.e., removal of toxic solutes) rather than being centered on the dialyzer, as is the case for the clearance-based parameter Kt/V.

In summary, these data show that dialysate kinetic measurements obtained by effluent urea monitoring compare favorably with the "gold standard" mDDQ method with little or no systematic bias. Indeed, the lower standard deviations for repeated testing with the DCM method suggest that this method is more reproducible. As expected, Kt/V values were lower than Kt/V values that were calculated by the single-pool VVSP method and are consistent with the expected lower whole-body urea clearance. When one considers the various measurement errors that can distort standard blood-side urea kinetics, dialysate-based kinetics should be seriously considered as the method of choice.

ACKNOWLEDGMENTS

The authors thank Jian Ruan for his help in validating the three-point solutions, and Jean Hayman for her help in manuscript preparation.

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Journal of the American Society of Nephrology 471