Hemodialysis Blood Access Flow Rates Can Be Estimated Accurately from On-Line Dialysate Urea Measurements and the Knowledge of Effective Dialyzer Urea Clearance

Robert M. Lindsay,* Jan Sternby,† Bo Olde,‡ Roland Persson,‡ Mary Ellen Thatcher,* and Kim Sargent*

*Optimal Dialysis Research Unit, London Health Sciences Centre, London, Ontario, Canada; and †Gambro AB Therapy Systems Research, Lyon, France, and Lund, Sweden

Measurement of blood flow rate (Qa) is used to monitor arteriovenous fistulas and grafts that are used for hemodialysis blood access. Most Qa measurements use indicator dilution techniques to measure the recirculation that is induced by the reversal of hemodialysis blood lines. R plus the dialysis circuit flow (Qb) allows the calculation of Qa. The principle of needle reversal also can be used with a dialysate urea monitor (e.g., DQM 200 [Gambro]) without injection of diluent; the effect of the reversal on urea concentration is observed. Access blood water flow rate (Qaw) in relation to the effective clearance (K) is found from the urea concentrations in the dialysate with needles in the normal (Cn) and reverse (Cr) positions: K/Qaw = (Cn - Cr)/Cr. Qa is calculated by adjusting Qaw for hematocrit and protein. For testing of this theoretical relationship, 20 patients who were dialyzed on Integra (Hospal) and Centrsytem 3 (Cobe) machines that were fitted with DQM 200 were studied. During each treatment, lines were reversed and Qa was measured by ultrasound velocity dilution (Transonic HD01 monitor); at the same time, Cn and Cr were measured by DQM 200 and K was calculated. K1 was determined from a predialysis blood urea concentration (Cb), initial dialysate urea concentration (Cd), dialysate flow rate (Qd), and the relationship K = Qd × Cd. K was determined separately from a conductivity step method using Diascan (Hospal) attached to Integra machines only (K2). With the use of K1, 127 comparisons were made; a correlation existed (r = 0.916), although Bland-Altman analysis showed that the dialysate urea method gave a mean value 5.3% ± 15.3% (±SD) higher than that of Transonic (P < 0.001). With the use of K2, there also was a correlation of (r = 0.944; n = 63), and Bland-Altman testing showed an NS difference of +3.5% between the dialysate urea and Transonic methods. Qa can be estimated from on-line dialysate urea measurements that are taken before and after line reversal together with knowledge of K.


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he measurement of blood access flow rate (Qa; ml/min) in arteriovenous fistulas and grafts that are used for hemodialysis (HD) blood access is becoming increasingly widespread. Reduced or falling levels for Qa have been found to correlate with access dysfunction and to predict subsequent access failure by thrombosis (1). The majority of Qa measurements use indicator dilution techniques to measure the amount of recirculation that is induced by the reversal of the arterial and venous dialysis lines. The knowledge of this plus the dialyzer flow rate (Qb; ml/min) allows the calculation of Qa (1). The most commonly used method to carry out the Qa measurement involves ultrasound velocity measurements of the flowing blood and their dilution by a saline bolus using the Transonic Hemodialysis Monitor (Transonic Inc., Ithaca, NY). Details of this and other technologies are given elsewhere (2). Because access recirculation will lead to a dilution of the urea content in the dialyzer arterial line as a result of blood of a lower urea content coming from the dialyzer venous line and because the degree of recirculation is inversely related to the Qa (3), we hypothesized that needle reversal can be used with a dialysate urea monitor without injection of diluent to measure Qa by observing the effect of the reversal on urea concentrations.

The access blood water flow rate (Qaw; ml/min) in relation to the effective urea clearance by the dialyzer (K; ml/min) can be found from the urea concentrations in dialysate with the needles in the normal (Cn) and reverse (Cr) positions. K will have to be corrected for the amount of ultrafiltration (ml/min) that occurs at the time of measurements. Therefore, (K - UF)/Qaw = (Cn - Cr)/Cr (equation 1).

The likelihood that equation 1 is correct comes from the work of Mercadal et al. (4). Those authors derived the same formula but with dialysate urea concentrations (Cd) replaced by dialysate values (in normal and reversed line positions, respectively). The Cd, however, are proportional to the dialysance values. They reflect the same effective ionic or urea clearances; we have already shown that these two clearances are the same (5). Therefore, we hypothesize the correctness of equation 1. Qa then can be calculated by correction of Qaw for hematocrit
Materials and Methods

**Dialysate-Based Urea Monitor**

The monitor used in these studies was the DQM 200 (Gambro Lundia AB, Lund, Sweden). It is an example of a urea monitor that measures on the basis of quantification of the conductivity increase that has occurred by the breakdown of urea by the enzyme urease. The monitor is placed after the dialysis machine in the spent dialysate line that goes to the drain. A small sample flow is split into two channels, one of which is directed through a urease column. The conductivity difference is measured between one cell in each channel. Both channels pass the same heat exchanger before the conductivity cells to keep temperatures equal so as to minimize temperature-induced errors. Carbon dioxide also is added before the urease column to keep the dialysate pH below 7, which is sufficient to ensure that the reaction products are in ionic form. This also is an ideal working pH for the urease. The result is a linear and accurate response over a large measuring range. More detail of the urea measurement by this and other urea monitors is given elsewhere (7).

**Effective Urea Clearance Measurement**

Effective urea clearance measurement was carried out in two ways. The transport rate of urea across the dialyzer membrane must be equal on both sides of the membrane. Therefore, Cb and Cd at any time during HD are related in the same proportion as Qd and the K. If Cb, Cd, and Qd are known or measured, then K theoretically may be derived from the relationship K × Cb = Qd × Cd (equation 4). Qd is measured accurately by most dialysis machines, and Cd can be measured by a dialysate urea monitor. Cb can be measured by blood sampling. K also can be estimated by the use of a step in dialysate conductivity (EID). This method, which has been described already, will take into account access and cardio-pulmonary recirculation and thus measures the effective clearance (K_{eff}). The K_{eff} has been shown to agree well with blood water urea and dialysate urea clearances when these also have been corrected for recirculation (access and cardiopulmonary) (5). During the first minute of HD, the urea concentration will decrease rapidly as recirculation develops. Because the urea concentration in dialysate that is measured by some urea monitors such as the DQM 200 is from filtered dialysate (i.e., postdialysate machine), this first decrease cannot be captured. The starting value on the dialysate side therefore will refer to the situation after recirculation has developed. However, if K is measured by EID, then this is K_{eff} and, therefore, recirculation is accounted for. The measured Cb theoretically should agree with a calculated value for Cb using equation 4. This theoretical relationship already has been tested and proved by us (9). Therefore, the reverse situation will hold true, namely that K can be calculated from a measured predialysis Cb and applied to equation 4.

**Study Design**

The study was a single-center, open-study design; 20 patients who were undergoing renal replacement therapy by HD were studied while they were undergoing dialysis using both Integra dialysis machines that were fitted with the Diamican device and by Centrysystem 3 (Gambro Healthcare, Lakewood, CO) machines without the Diamican device. During each dialysis, a DQM 200 urea monitor was fitted. Each patient was to have two Integra and two Centrysystem 3 treatments during a 4-wk period. During each dialysis treatment, two periods occurred when lines were reversed and Qa measurements were made to provide a theoretical maximum of 160 data points. The 4-wk period was preceded by a 1-wk familiarization phase during which staff training on the equipment and study procedures took place.

**Patients**

The study was approved by the Ethics Review Board of The University of Western Ontario, and written informed consent was obtained from all participating patients. The 20 patients (10 men, 10 women) all had end-stage renal failure and were undergoing dialysis routinely in the Adam Linton Dialysis Unit of London Health Sciences Centre. All patients were selected to have arteriovenous accesses (14 arteriovenous fistulas and six synthetic grafts) that were known to be functioning well and had previously been shown to have Qa in excess of 750 ml/min and hence were believed to have zero access recirculation under normal dialysis conditions. The access flow and recirculation measurements were carried out using the Transonic HD01 monitor. In addition, all patients met the following inclusion criteria: Older than 18 yr, receiving chronic renal replacement therapy for > 3 mo, and known to have end-stage renal failure and were undergoing dialysis routinely in the Adam Linton Dialysis Unit of London Health Sciences Centre. All patients were selected to have arteriovenous accesses (14 arteriovenous fistulas and six synthetic grafts) that were known to be functioning well and had previously been shown to have Qa in excess of 750 ml/min and hence were believed to have zero access recirculation under normal dialysis conditions. The access flow and recirculation measurements were carried out using the Transonic HD01 monitor. In addition, all patients met the following inclusion criteria: Older than 18 yr, receiving chronic renal replacement therapy for > 3 mo, and known to have a well-regulated anticoagulant regimen during dialysis therapy. Before selection, each patient had been demonstrated to be free from any of the following exclusion criteria: Known serious cardiovascular instability therapy during dialysis, active malignancy, known HIV/AIDS, known hepatitis B or C, pregnancy, and participation in other studies.

**HD Treatments**

They were as routine for each individual patient so that the regular dialysis prescription was followed. Each patient received dialysis by either an F80 (n = 6) or an F8 (n = 14) polysulphone membrane dialyzer...
(Fresenius Inc., Lakewood, CO). The blood flow rate for the treatment was chosen so that it could be kept constant throughout the dialysis procedure and to meet the patient’s prescription requirements. A constant ultrafiltration rate also was chosen, the actual rate varying according to the individual patient’s needs. When believed to be clinically necessary, changes in ultrafiltration rate were permissible, provided that the rate was stabilized and constant during the periods when measurements were made. Likewise, when for clinical reasons the blood flow rate had to be reduced during the course of dialysis, care was taken to ensure that these were held constant during measurement periods.

**Diascan Measurements**

Diascan measurements are made automatically at 30-min intervals during the dialysis treatment. K values that were given by the Diascan at times when the initial blood flow rate was in effect all were recorded, and the average value was taken for further calculations.

**Dialysate Urea**

The initial Cd measured by the DQM 200 was taken and recorded. Likewise, during the two measurement phases, the Cd was taken just before (Cn) and after reversal of blood lines (Cr), and these were recorded.

**Qa by Transonic Monitor**

After each period with line reversal and after Cr was recorded and the lines were normalized once more, a measurement of Qa was made by ultrasound velocity dilution using the Transonic HD01 monitor, and this result was recorded. When a value for Qa was found to be within 100 ml/min of the dialysis circuit blood flow rate (Qb) or less, a measurement of access recirculation also was made using the Transonic HD01 monitor.

**Blood Samples**

Blood was drawn from the access arterial needle before the dialysis treatment was initiated to measure Tp (g/L) and urea (mmol/L). Blood samples also were taken just before the reversal of blood lines for the measurement of Hct (U) and for Tp (g/L). The samples were sent immediately to the hospital laboratory for analysis. Urea was analyzed using the Paramax nitrogen reagent (Dade Diagnostics of PI Inc., Guada, Puerto Rico), Tp levels were analyzed using the Paramax total protein reagent (Baxter Diagnostics Inc., Deerfield, IL), and Hct on blood samples was determined by microcentrifugation. Predialysis plasma urea (P urea) values were corrected for Tp concentration to give plasma water concentration (PW urea) according to the relationship PW urea = P urea/(1 – Tp/1000) (equation 5). This PW urea value then was taken to determine K from the relationship in equation 4. This K value is referred to as K1. The Tp concentration together with the Hct was taken to determine K from the relationship in equation 4. K2 was determined separately from the mean of Diascan measurements taken when the initial (prescribed) blood flow rate was in effect. This was obtainable only with dialysis using the Integra machine. Qa values that were calculated with both K1 and K2 were compared with the measured Qa values that were obtained by the Transonic monitor, which for this study is regarded as the “gold standard.”

**Statistical Analyses**

Data are presented as mean ± SD. Comparisons between methods are made using linear regression and Bland-Altman analyses.

**Results**

Although the 20 patients each were planned for two Centrysystem 3 and two Integra dialysis treatments, there actually were 38 dialysis treatments with the Centryystem 3 and 42 with the Integra. With each dialysis treatment, there were two periods with reversed lines to allow measurements to take place, leading to a maximum of 160 comparisons. Data were discarded when duplicate Qa readings that were made by the Transonic monitor were not within 10% of each other, and this occurred on 15 occasions; when access recirculation was detected without line reversal, which occurred on six occasions; and when DQM 200 technical failures occurred, which happened on 12 occasions. This left 127 comparisons: 60 with the Centrysystem 3 machine and 67 using the Integra machine. Using K1 and 127 comparisons, a highly significant correlation between the calculated value for Qa and the Qa by the Transonic monitor, was obtained (r = 0.92; P < 0.0001). These data are shown over the line of identity in Figure 1. The scatter plots in Figure 1 do suggest that the calculated value for Qa may slightly overestimate the gold standard that was obtained by the Transonic monitor. Bland-Altman–like analysis of these data is shown in Figure 2, which demonstrates the percentage difference between the calculated and Transonic measured Qa values plotted against the mean of access flows that were obtained with the two methods. Figure 2 shows separately the plots for both the Cobe Centrysystem 3 machine and the Integra system 3 and two Integra dialysis treatments, there actually were 38 dialysis treatments with the Centryystem 3 and 42 with the Integra. With each dialysis treatment, there were two periods with reversed lines to allow measurements to take place, leading to a maximum of 160 comparisons. Data were discarded when duplicate Qa readings that were made by the Transonic monitor were not within 10% of each other, and this occurred on 15 occasions; when access recirculation was detected without line reversal, which occurred on six occasions; and when DQM 200 technical failures occurred, which happened on 12 occasions. This left 127 comparisons: 60 with the Centrysystem 3 machine and 67 using the Integra machine. Using K1 and 127 comparisons, a highly significant correlation between the calculated value for Qa and the Qa by the Transonic monitor, was obtained (r = 0.92; P < 0.0001). These data are shown over the line of identity in Figure 1. The scatter plots in Figure 1 do suggest that the calculated value for Qa may slightly overestimate the gold standard that was obtained by the Transonic monitor. Bland-Altman–like analysis of these data is shown in Figure 2, which demonstrates the percentage difference between the calculated and Transonic measured Qa values plotted against the mean of access flows that were obtained with the two methods. Figure 2 shows separately the plots for both the Cobe Centrysystem 3 machine and the Integra machine. In total, there was a significant 5.28% (P < 0.001) overread of the access flow by the calculated method. The actual machine used was irrelevant as far as this difference was concerned (Centrysystem machine 5.16% difference; Integra machine 5.39% difference). Using K2, there also was a highly statistically significant correlation between the calculated Qa value and the Qa that was found using the Transonic monitor.

Figure 1. Comparison of calculated and Transonic access flow rates when K1 is used in equation 1.
(r = 0.94; P < 0.0001). These data are shown in Figure 3; here, Bland-Altman–like testing showed an NS difference of +3.5% between calculated and measured values, and there was no change in this difference over the range of access flows.

**Discussion**

The primary objective of this study was to test the theory that blood access flow could be measured by examination of the change of the urea concentration in the spent dialysate after line reversal, provided that the effective K is known. We hypothesized that the relationship between the access Qaw (ml/min) and the effective K (ml/min) are found from the urea concentrations in dialysate with the needles in normal (Cn) and reversed (Cr) position. K must be corrected for the amount of ultrafiltration (ml/min) that occurs at the time of measurement. Therefore (K – UF)/Qaw = (Cn – Cr)/Cr. The Qa (ml/min) then can be calculated by correction of Qaw for Hct and Tp concentration. We calculated K by two separate methods. One was from Cb, the initial Cd, the Qd, and the relationship K × Cb = Qd × Cd. K also was determined from a conductivity step method using the Diascan attached to the Integra dialysis machine. We previously showed that the EID correlates very closely with blood water side urea clearances and almost exactly with dialysate side urea clearances when the clearances were corrected for recirculation (5). The results of these studies show that when this latter method of measuring effective clearance is used, the Qa values that are obtained from the Cd are highly correlated with those that use the gold standard Transonic method and that Bland-Altman testing shows that there is no significant difference between the dialysate urea and the Transonic methods over the range of access flows studied.

Using the effective clearance calculated from the relationship K × Cb = Qd × Cd, there also was a strong correlation of Qa values that were obtained from Cd with the Transonic method. Here, however, the dialysate urea method gave a mean value of 5.3% higher than the value that was obtained with Transonic. We have no obvious explanation for this. It is possible that the effective K at the start of dialysis is not constant and does decline over the course of dialysis. K1 was derived at the start of dialysis and assumed to be constant, whereas K2 (obtained by Diascan) was recorded near the time of each access flow measurement. An overestimation of effective clearance will overestimate access Qaw (equation 1). The test repeatability for access blood flow measurements by the Transonic method has been reported at 13% (10). This variability will not explain the overestimation. It does, however, point out that there is no absolute gold standard for access blood flow measurement, and exact correlations between methods used in clinical testing are impossible. Nevertheless, these results prove the correctness of equation 1 and certainly prove the original hypothesis that the access Qaw in relationship to the effective clearance by the dialyzer can be found from the urea concentrations in dialysate with the needles in normal and reversed positions. The study was not designed to test the reproducibility of this method of measuring Qa. Although two measurements were taken during each dialysis treatment, they were of necessity >30 min apart (EID measurements are taken at 30-min intervals using Diascan).
can) and steady-state conditions of flow could not be guaranteed. Nevertheless, the scatter plots of data shown in Figures 1 and 3 suggest that method reproducibility is as good as that of the Transonic access flow measurement, which is of proven reproducibility (10). Note, also, that data were discarded when duplicate Qa readings that were made by the Transonic monitor were not within 10% of each other. The information adds to the development of on-line monitoring technologies that are able to provide Qa accurately and automatically without injections, and if automatic pump reversal could be done by the dialysis machine, then no intervention by the nurse operator would be required.

How practical this described method is in a busy dialysis clinic is, of course, uncertain. A urea sensor on its own cannot measure Qa. Because these experiments have shown that the knowledge of effective K is necessary and, thus, that the urea sensor will require the addition of either blood urea sampling or a device that measures ionic dialysance, urea monitors as used in these experiments have not gained widespread acceptance anywhere in the world and tend to be regarded as tools for researchers. They have an inherent cost and the need for maintenance with their use, which certainly will inhibit usage growth. As a researcher’s tool, there is no question that they have an undisputed place and provide a world of possibilities for new and exciting areas of measurement in the fields of dialysis adequacy and nutrition (7). The measurement of EID by conductivity-based techniques is, however, very cheap, requiring only one or two conductivity cells added to the dialysate circuit. These conductivity cells are very accurate and rugged, and the device requires little maintenance. The use of EID as a surrogate for urea monitoring using a device such as the Diascan is gaining acceptance, and, theoretically, such a device on its own should be able to be used to measure access flow. The equation 1 as we derived obviously comes from the work of Mercadal et al. (4), who derived the same formula but with Cd replaced by dialysance values as indicated in the beginning of this article. Cd must be proportional to dialysance values because they reflect the same effective ionic or urea clearances. Fresenius, with their latest machine (2008K), actually has incorporated software that will give a value for Qa using this technology. Its accuracy and validity, however, have not been established, and more work needs to be done in this area.

References