# Hemodialyzer mass transfer-area coefficients for urea increase at high dialysate flow rates

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**Hemodialyzer mass transfer-area coefficients for urea increase at high dialysate flow rates.** The dialyzer mass transfer-area coefficient ($K_oA$) for urea is an important determinant of urea removal during hemodialysis and is considered to be constant for a given dialyzer. We determined urea clearance for 22 different models of commercial hollow fiber dialyzers ($N = \sim5$/model, total $N = 107$) *in vitro* at 37°C for three countercurrent blood ($Q_b$) and dialysate ($Q_d$) flow rate combinations. A standard bicarbonate dialysis solution was used in both the blood and dialysate flow pathways, and clearances were calculated from urea concentrations in the input and output flows on both the blood and dialysate sides. Urea $K_oA$ values, calculated from the mean of the blood and dialysate side clearances, varied between 520 and 1230 ml/min depending on the dialyzer model, but the effect of blood and dialysate flow rate on urea $K_oA$ was similar for each. Urea $K_oA$ did not change ($690 \pm 160$ vs. $680 \pm 140$ ml/min, $P = NS$) when $Q_b$ increased from $306 \pm 7$ to $459 \pm 10$ ml/min at a nominal $Q_d$ of 500 ml/min. When $Q_d$ increased from $504 \pm 6$ to $819 \pm 8$ ml/min at a nominal $Q_b$ of 450 ml/min, however, urea $K_oA$ increased ($P < 0.001$) by $14 \pm 7\%$ (range 3 to 33%, depending on the dialyzer model) to $780 \pm 150$ ml/min. These data demonstrate that increasing nominal $Q_d$ from 500 to 800 ml/min alters the mass transfer characteristics of hollow fiber hemodialyzers and results in a larger increase in urea clearance than predicted assuming a constant $K_oA$.

Accurate prediction of dialyzer urea clearance during hemodialysis is essential when prescribing therapy using urea kinetic modeling. Clearance of urea from the dialyzer depends on the flow conditions (blood, dialysate and ultrafiltration flow rates) and properties of the dialysis membrane, such as surface area and intrinsic diffusive capacity [1, 2]. The latter two parameters are difficult to measure individually; therefore, only their multiplicative product is evaluated and is called the mass transfer-area coefficient ($K_oA$). While previous studies have demonstrated that dialyzer $K_oA$ values can be a complex function of several design parameters [3], urea $K_oA$ values for modern hollow fiber dialyzers are considered to be constant during routine clinical hemodialysis. When urea $K_oA$ is constant and accurately known, it is possible to predict dialyzer urea clearance from $K_oA$ and the blood, dialysate and ultrafiltration flow rates using known theoretical relationships [1, 2].

The variation of dialyzer urea $K_oA$ under routine clinical

operating conditions has not, however, been studied extensively. Furthermore, the accuracy of nominal values of urea clearance and $K_oA$ provided by dialyzer manufacturers has recently been questioned [4]. In the present study, we determined urea clearance and $K_oA$ for 22 different dialyzer models under identical *in vitro* test conditions and determined the dependence of urea $K_oA$ on blood and dialysate flow rates.

## Methods

### Hemodialyzers

The dialyzers tested in this study comprised 22 different models proposed for use in the multicenter Hemodialysis (HEMO) Study sponsored by the U.S. National Institutes of Health [5]. Each manufacturer was requested to supply one dialyzer from five different lots with manufacturing dates that were as far apart as possible for each model. It was, however, impractical for some manufacturers to provide dialyzers from the requested number of lots within the designated time period. The dialyzer models provided by the manufacturers are shown in Table 1.

### Evaluation of dialyzer urea clearance

A 2008E dialysis machine (Fresenius USA, Concord, CA, USA) equipped with an ultrafiltration controller was used to prepare the bicarbonate solution for the blood compartment and to circulate fluids through both the blood and dialysate flow pathways. The bicarbonate solution for the blood compartment was freshly prepared immediately before each experiment from a concentrate (Naturalyte® with a potassium concentration of 2.0 mEq/liter; National Medical Care, Rockleigh, NJ, USA) and was placed in a large reservoir of approximately 80 liters. Urea (Catalog No. U5128; Sigma Chemical, St. Louis, MO, USA) was then added to the blood reservoir such that the urea nitrogen concentration was approximately 90 (range 87 to 94) mg/dl. The temperature of the reservoir solution was continuously maintained at 37°C by a circulating heater (Thermomix® UB; Braun, Melsungen, Germany). The solution for the dialysate flow pathway was generated on-line from concentrate by the dialysis machine during the experiment and was identical in composition to that in the blood flow pathway except that it was devoid of urea. The solutions for both pathways circulated separately in single pass, countercurrent fashion.

Urea clearances were measured at three different nominal blood and dialysate flow rate combinations (Table 2). These flow

**Table 1.** Dialyzer models studied and data provided by the manufacturers

| Manufacturer | Model | Different lots | Surface area $m^2$ |
|---|---|---|---|
| Althin | Altrex-140 | 1 | 1.4 |
| | AltraNova 200 | 1 | 2.0 |
| Asahi | PAN 85DX | 1 | 1.7 |
| | PAN 110DX | 1 | 2.2 |
| Baxter | CA150 | 5 | 1.5 |
| | CA170 | 5 | 1.7 |
| | CA210 | 5 | 2.1 |
| | CT110G | 3 | 1.1 |
| | CT190G | 4 | 1.9 |
| Fresenius | F6 | 4 | 1.3 |
| | F8 | 5 | 1.8 |
| | F50 | 4 | 1.0 |
| | F60A | 3 | 1.3 |
| | F60B | 1 | 1.3 |
| | F80A | 4 | 1.8 |
| | F80B | 2 | 1.8 |
| Renal Systems | Primus 1350 | 5 | 1.35 |
| | Primus 2000 | 5 | 1.98 |
| Toray | Filtryzer B2-1.5H | 3 | 1.5 |
| | Filtryzer B2-2.0 | 3 | 2.02 |
| | Filtryzer B1-2.1U | 2 | 2.1 |
| | Filtryzer BK-2.1U | 3 | 2.1 |

**Table 2.** Nominal and measured blood ($Q_b$) and dialysate ($Q_d$) flow rates in the present study

| Combination | | $Q_b$ ml/min | $Q_d$ ml/min |
|---|---|---|---|
| 1 | nominal | 300 | 500 |
| | measured | $306 \pm 7$ | $508 \pm 30$ |
| 2 | nominal | 450 | 500 |
| | measured | $459 \pm 10$ | $504 \pm 6$ |
| 3 | nominal | 450 | 800 |
| | measured | $458 \pm 11$ | $819 \pm 8$ |

Measured flow rates are reported as mean $\pm$ SD.

nitrogen concentration in the blood inlet (arterial), $C_{bo}$ denotes the urea nitrogen concentration in the blood outlet (venous), and $C_{do}$ denotes the urea nitrogen concentration in the dialysate outlet. Overall urea mass balance, comparing the blood side and the dialysate side clearances (blood minus dialysate), was $-0.7 \pm 2.1$ (SD)% over 321 clearance determinations.

Urea $K_oA$ was calculated from the mean of the blood and dialysate side urea clearances ($K_d$) using the following equation for countercurrent blood and dialysate flows [6]

$$K_oA = \frac{Q_b Q_d}{Q_b - Q_d} \ln\left[\frac{1 - K_d/Q_b}{1 - K_d/Q_d}\right]$$

where ln denotes the natural logarithm. For each flow rate combination, the mean $K_oA$ value for the three separate estimates corresponding to the triplicate sample collections were averaged to obtain a single value for each tested dialyzer.

### Statistics

Three to six dialyzers of each model were tested, and variability among the tested dialyzers was expressed as the standard deviation (SD). Comparison among urea $K_oA$ values for the three flow rate combinations was performed using analysis of variance. Further comparisons among the individual flow rate combinations were performed using a Student's paired *t*-test corrected for multiple comparisons by the Bonferroni method [7].

### Results

Measured blood and dialysate flow rates approximated the nominal values (Table 2), and the variability of the measured flow rates among experiments was small. Measured urea $K_oA$ at the three flow rate combinations for all dialyzer models combined are shown in Figure 1. Urea $K_oA$ values at nominal blood flow rates of 300 and 450 ml/min were similar when the nominal dialysate flow rate was constant at 500 ml/min; however, these urea $K_oA$ values were significantly lower than those obtained when the nominal dialysate flow rate was increased to 800 ml/min.

Table 3 lists urea $K_oA$ for each dialyzer model at nominal dialysate flow rates of 500 and 800 ml/min. Urea $K_oA$ increased by an average of $14 \pm 7\%$ when the nominal dialysate flow rate increased from 500 to 800 ml/min; however, this increase was variable among dialyzer models (range 3 to 33%). The urea $K_oA$ values determined in this study at a nominal dialysate flow rate of 500 ml/min were $92 \pm 10\%$ (range 76 to 119%) of those provided by the manufacturers after correcting the latter values for ultrafiltration.

Figure 2 plots values of urea $K_o$, calculated by dividing urea $K_oA$ at a nominal dialysate flow rate of 500 ml/min (Table 3) by
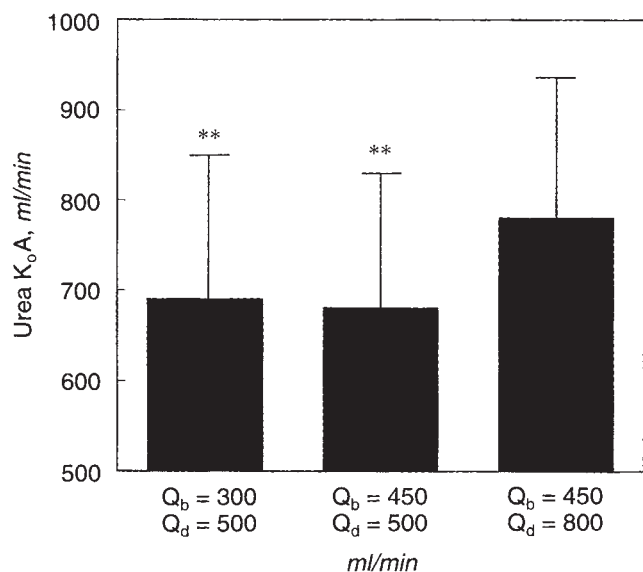
rate combinations were chosen to determine separately the effect of increasing nominal blood flow rate from 300 to 450 ml/min (comparing combination 1 with 2) and that of increasing nominal dialysate flow rate from 500 to 800 ml/min (comparing combination 2 with 3). While the dialysate flow rates were chosen to span those employed during routine hemodialysis, the blood flow rates were chosen at the high end of those used clinically, since use of a high blood flow rate produces more accurate estimates of $K_oA$ for solutes whose transport is limited primarily by the blood flow rate, such as urea. Urea clearance determinations were performed at the flow rate combinations in random order, and the ultrafiltration flow rate was kept at zero during each experiment.

The blood flow rate ($Q_b$) and the dialysate flow rate ($Q_d$) were both directly measured by two-minute timed collections of the outflow from the respective pathways. Samples were then obtained using needles and syringes in rapid succession from the dialysate outlet, venous tubing, and arterial tubing (in that order) three separate times. The samples were kept at 4°C and assayed within 28 hours for urea nitrogen.

### Analytical

The concentration of urea nitrogen in all samples was determined by an automated enzymatic assay (CX7; Beckman, Fullerton, CA, USA). Calibration curves, over the urea nitrogen concentration range from 10 to 100 mg/dl, were generated 11 times throughout this study using the same bottle of urea employed for all experiments. Each urea nitrogen concentration was corrected using the average calibration curve.

### Data analyses

Both blood side and dialysate side urea clearances were calculated using standard formulae [1]. Blood side clearance was calculated as $(C_{bi} - C_{bo}) \times (Q_b/C_{bi})$, and dialysate side clearance was calculated as $C_{do} \times (Q_d/C_{bi})$, where $C_{bi}$ denotes the urea

**Fig. 1.** *Urea $K_oA$ values determined under three different flow rate combinations for all studied dialyzer models combined.* The error bars denote one SD. $K_oA$ values were lower (**$P < 0.001$) at a nominal dialysate flow rate of 500 than at a nominal rate of 800 ml/min.



**Fig. 2.** *Urea $K_o$ values, calculated by dividing urea $K_oA$ at a nominal dialysate flow rate of 500 ml/min (Table 3) by the dialyzer surface area (Table 1), plotted versus surface area for 6 different series of dialyzers.* Each series of dialyzers were obtained from the same manufacturer; they have the same hollow fiber design and membrane material but different surface areas. (●) denotes PAN dialyzers from Asahi; (○) denotes CA dialyzers from Baxter; (■) denotes CT dialyzers from Baxter; (□) denotes F6 and F8 dialyzers from Fresenius; (▲) denotes F50, F60, and F80 dialyzers from Fresenius; (♦) denotes Primus dialyzers from Renal Systems.

**Table 3.** Dialyzer urea $K_oA$ determined at two different dialysate flow rates ($Q_d$) in the present study

| Manufacturer | Model | N | $Q_d =$ 500 ml/min | $Q_d =$ 800 ml/min |
|---|---|---|---|---|
| Althin | Altrex-140 | 5 | 530 ± 20 | 630 ± 20 |
| | AltraNova 200 | 5 | 620 ± 40 | 710 ± 50 |
| Asahi | PAN 85DX | 5 | 560 ± 80 | 700 ± 80 |
| | PAN 110DX | 5 | 570 ± 140 | 700 ± 140 |
| Baxter | CA150 | 5 | 630 ± 40 | 690 ± 30 |
| | CA170 | 6 | 680 ± 50 | 760 ± 20 |
| | CA210 | 6 | 910 ± 80 | 970 ± 70 |
| | CT110G | 4 | 690 ± 70 | 790 ± 70 |
| | CT190G | 5 | 1070 ± 50 | 1230 ± 40 |
| Fresenius | F6 | 5 | 560 ± 20 | 620 ± 20 |
| | F8 | 5 | 720 ± 40 | 810 ± 40 |
| | F50 | 5 | 520 ± 20 | 590 ± 20 |
| | F60[a] | 7 | 630 ± 10 | 700 ± 10 |
| | F80[a] | 9 | 750 ± 50 | 860 ± 50 |
| Renal Systems | Primus 1350 | 5 | 550 ± 50 | 660 ± 60 |
| | Primus 2000 | 5 | 610 ± 100 | 760 ± 80 |
| Toray | Filtryzer B2-1.5H | 5 | 610 ± 10 | 640 ± 10 |
| | Filtryzer B2-2.0 | 5 | 760 ± 20 | 800 ± 20 |
| | Filtryzer B1-2.1U | 5 | 840 ± 10 | 910 ± 20 |
| | Filtryzer BK-2.1U | 5 | 840 ± 20 | 910 ± 20 |

Values are listed as mean ± SD. The results at blood flow rates of 300 ml/min and 450 ml/min at a $Q_d$ of 500 ml/min were combined.

[a] Results for the A and B models of the F60 and F80 dialyzers were similar and were averaged

the nominal dialyzer surface area (Table 1), versus surface area for six different series of dialyzers. The different models of each dialyzer series were from the same manufacturer; they have the same hollow fiber design and membrane material but different surface areas. For each series of dialyzers except one, urea $K_o$ decreased with increasing surface area, demonstrating a decrease in urea transfer efficiency per unit surface area.
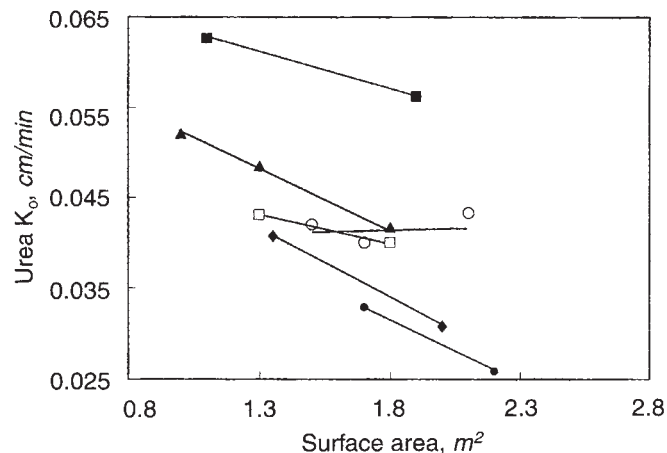
## Discussion

### Dialyzer mass transfer characteristics for urea

The dialyzer mass transfer-area coefficient characterizes the permeability of the mass transfer barrier between the blood and dialysate pathways of a hemodialyzer. Previous work [3] has shown that the overall mass transfer resistance of this barrier comprises the dialysis membrane and stagnant fluid (or boundary) layers adjacent to the membrane in the blood and dialysate flow pathways. Indeed, small solute transfer in early dialyzers (of the 1960s and 1970s) was significantly limited by stagnant fluid layers in both the blood and dialysate flow pathways. Improvements in dialyzer design have reduced the importance of mass transfer resistances from blood and dialysate stagnant fluid layers such that urea mass transfer-area coefficients are largely determined by the surface area and the intrinsic permeability of the dialysis membrane. Thus, urea mass transfer-area coefficients of modern hollow fiber dialyzers are considered to be constants.

Increasing the blood or dialysate flow rate decreases the thickness of the respective stagnant fluid layer [3]. Urea $K_oA$ for each dialyzer model was independent of blood flow rate, demonstrating that the stagnant fluid layer in the blood flow pathway was not significant in limiting overall urea transfer. It should be cautioned, however, that this inference is not necessarily applicable to clinical dialysis where whole blood, a more viscous and complex fluid than dialysis solution, is perfusing the blood pathway. The increase in urea $K_oA$ with increasing dialysate flow rate suggests that the dialysate stagnant fluid layer provides a significant resistance to urea transfer. It is also possible, however, that the increase in urea $K_oA$ with increasing dialysate flow rate results from an improved distribution of flow in the dialysate compartment [8].

Allen, Frost and Hoenich [9] have recently shown that an increase in dialysate flow rate can result in a reduced overall resistance to urea transfer (or an increase in urea $K_oA$) in two

**Table 4.** Predicted percent increase in urea clearance (%$\Delta K_d$) and absolute urea clearance ($K_d$) in ml/min for three hypothetical dialyzers upon increasing the nominal dialysate flow rate ($Q_d$) from 500 to 800 ml/min

| Dialyzer | $K_0A$ (and $K_d$) at $Q_d$ of 500 ml/min | %$\Delta K_d$ (and $K_d$) if $K_0A$ is constant | %$\Delta K_d$ (and $K_d$) if $K_0A$ increases by 14% | %$\Delta K_d$ (and $K_d$) if $K_0A$ increases by 33% |
|---|---|---|---|---|
| Assuming a nominal blood flow rate ($Q_b$) of 300 ml/min | | | | |
| 1 | 500 (211) | 6 (224) | 12 (235) | 17 (248) |
| 2 | 700 (238) | 6 (252) | 10 (262) | 14 (272) |
| 3 | 900 (256) | 5 (269) | 8 (277) | 11 (284) |
| Assuming a nominal blood flow rate ($Q_b$) of 450 ml/min | | | | |
| 1 | 500 (243) | 9 (265) | 16 (283) | 25 (304) |
| 2 | 700 (282) | 10 (311) | 16 (328) | 23 (342) |
| 3 | 900 (310) | 11 (343) | 16 (358) | 21 (375) |

**Table 5.** Predicted single pool urea Kt/V for a hypothetical patient with a urea distribution volume of 50 liters (neglecting urea rebound) who was dialyzed for four hours using three hypothetical dialyzers upon increasing the nominal dialysate flow rate ($Q_d$) from 500 to 800 ml/min

| Dialyzer | Urea Kt/V at $Q_d$ of 500 ml/min | Urea Kt/V if $K_0A$ is constant | Urea Kt/V if $K_0A$ increases by 14% | Urea Kt/V if $K_0A$ increases by 33% |
|---|---|---|---|---|
| Assuming a nominal blood flow rate ($Q_b$) of 300 ml/min | | | | |
| 1 | 1.01 | 1.08 | 1.13 | 1.19 |
| 2 | 1.14 | 1.21 | 1.26 | 1.31 |
| 3 | 1.23 | 1.29 | 1.33 | 1.36 |
| Assuming a Nominal Blood Flow Rate ($Q_b$) of 450 ml/min. | | | | |
| 1 | 1.17 | 1.27 | 1.36 | 1.46 |
| 2 | 1.35 | 1.49 | 1.57 | 1.64 |
| 3 | 1.49 | 1.65 | 1.72 | 1.80 |

types of hollow fiber dialyzers containing Cuprophan® membranes. Those studies were performed using dialysate flow rates over the range from 500 to 3000 ml/min, where the dialysate stagnant fluid layer was likely disrupted by turbulent dialysate flow. The results of the present study extend those observations to a large variety of hollow fiber dialyzers, and further demonstrate that increases in dialysate flow rate over a more limited and clinically relevant range can also increase urea $K_0A$.

The studies of Allen et al [9] also suggested that dialyzers containing large surface areas (by using more and longer hollow fibers) have decreased urea transfer efficiency per unit surface area. The results shown in Figure 2 support this concept and point out potential problems in the development of dialyzers with surface areas larger than those currently available. Such limitations, however, may be overcome to some extent by increasing dialysate flow rate as suggested by the results from this study. Since increasing dialysate flow rates increase the overall cost of dialysis treatments, future developments in dialyzer design that optimize dialysate flow patterns and effect a similar increase in dialyzer performance without requiring higher dialysate flow rates are eagerly anticipated.

### Clinical relevance

The effect of increasing dialysate flow rate on urea clearance assuming a constant value of urea $K_0A$ has been theoretically predicted by numerous investigators, most recently by Hootkins [10]. Such analyses have predicted that increasing dialysate flow rate from 500 to either 800 or 1000 ml/min only results in a small increase in urea clearance. Table 4 shows predicted increases in urea clearance based on the results of this study when dialysate flow rate is increased from 500 to 800 ml/min under three different conditions: when urea $K_0A$ remains constant at the higher dialysate flow rate; when urea $K_0A$ increases by 14% (the mean increase) at the higher dialysate flow rate; and when urea $K_0A$ increases by 33% (the maximum increase) at the higher dialysate flow rate. Predicted percent increases in urea clearance and absolute values of urea clearance are tabulated for three hypothetical dialyzers with different values of urea $K_0A$ assuming a blood flow rate of 300 and 450 ml/min. When urea $K_0A$ is constant, the increase in urea clearance is small, consistent with previous predictions [10]. When urea $K_0A$ increases with increasing dialysate flow rate, however, the predicted increase in urea

clearance can be substantially greater. Moreover, predicted increases in urea clearance as a result of increases in dialysate flow rate are more substantial at the higher blood flow rate. Table 5 shows these same predictions expressed as single pool urea Kt/V for a hypothetical patient who is dialyzed for four hours and has a urea distribution volume of 50 liters (neglecting urea rebound). These increases in urea clearance and single pool Kt/V are substantial and would permit significant increases in dialysis dose as assessed by urea kinetics given a fixed treatment time.

It should be emphasized that the present study only examined dialyzer urea clearance *in vitro* and these results cannot be translated directly into clinical dialysis without direct confirmation [4]. Preliminary studies suggest, however, that these *in vitro* results are also applicable to clinical dialysis using these same dialyzers [11]. In addition, the present data were obtained on only a sample of dialyzers from each manufacturer and are not necessarily representative of all the dialyzers in general clinical use. Variations in the dialyzer manufacturing process from lot to lot may produce variability in urea $K_0A$ values. Furthermore, effective urea clearance from the patient is influenced by factors other than dialyzer urea clearance, such as blood water content, vascular access recirculation, cardiopulmonary recirculation, and dialyzer reuse [12]. The extent to which increases in dialyzer urea clearance as described in this study will be reflected in clinical urea clearance depends significantly on these other parameters. Studies to test these relationships in the clinical setting will be forthcoming from the HEMO Study.

### Acknowledgments

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