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

JOHN K. LEYPOLDT, ALFRED K. CHEUNG, LAWRENCE Y. AGODOA, JOHN T. DAUGIRDAS, TOM GREENE, and PRAKASH R. KESHAVIAH, for the Hemodialysis (HEMO) Study

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

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 = ~5/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 ± 160 vs. 680 ± 140 ml/min, P = NS) when Q_b increased from 306 ± 7 to 459 ± 10 ml/min at a nominal Q_d of 500 ml/min. When Q_d increased from 504 ± 6 to 819 ± 8 ml/min at a nominal Q_b of 450 ml/min, however, urea K_oA increased ($P < 0.001$) by 14 ± 7% (range 3 to 33%, depending on the dialyzer model) to 780 ± 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.

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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

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

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 ± 7	508 ± 30
2	nominal	450	500
	measured	459 ± 10	504 ± 6
3	nominal	450	800
	measured	458 ± 11	819 ± 8

Measured flow rates are reported as mean ± 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 ± 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]

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

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 ± 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 ± 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