Effect of Low Dialysate Flow Rate on Hemodialyzer Mass Transfer Area Coefficients for Urea and Creatinine

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Recent work has shown that the dialyzer mass transfer area coefficient (K_oA) for urea increases when the dialysate flow rate is increased from 500 to 800 mL/min. In this study we determined urea and creatinine clearances for two commercial dialyzers containing polysulfone hollow fibers in vitro at 37°C, a nominal blood flow rate of 300 mL/min, and dialysate flow rates (Q_d) ranging from 100 to 800 mL/min. A standard bicarbonate dialysis solution was used in both the blood and dialysate flow pathways, and clearances were calculated from solute concentrations in the input and output flows on both the blood and dialysate sides. Urea and creatinine K_oA values, calculated from the mean of the blood and dialysate side clearances, increased ($p < 0.01$) with increasing Q_d over the entire range studied. The increase in both urea and creatinine K_oA with increasing Q_d was proportional to the K_oA value. These data show that changes in Q_d alter small solute clearances greater than predicted assuming a constant K_oA.

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Key words

Clearance, creatinine, dialysate, flow, hemodialyzer, urea

Introduction

An accurate prediction of dialyzer urea clearance is an essential element of the hemodialysis prescription [1]. Clearance of urea from the dialyzer depends on the blood, dialysate, and ultrafiltration flow rates and the mass transfer area coefficient (K_oA) for urea [2]. While urea K_oA values for a given dialyzer model are often considered to be independent of the flow conditions, recent work has shown that this parameter increases when the dialysate flow rate is increased from 500 to 800 mL/min [3]. This effect was observed for all dialyzers studied to date, but the extent of the increase in urea K_oA depended on the dialyzer model.

Alternative hemodialysis strategies have recently been proposed where dialyzers are operated under flow conditions that are not routinely assessed by manufacturers [4,5]; one of these alternatives, nocturnal hemodialysis, uses dialysate flow rates less than 500 mL/min [6–8]. The current study was designed to examine the effect of the dialysate flow rate on urea and creatinine K_oA values over the dialysate flow rate range from 100 to 800 mL/min.

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Material and methods

Hemodialyzers

The dialyzers tested in this study were two different models containing low flux, polysulfone hollow fibers with different membrane surface areas: F5 and F8 dialyzers (Fresenius Medical Care North America, Ogden, UT, U.S.A.). The former contains 1.0 m^2 and the latter 1.8 m^2 of nominal membrane surface area.

Evaluation of dialyzer urea and creatinine clearances

The details of the experiments performed in this study were essentially identical to those described previously [3]. A 2008E dialysis delivery system (Fresenius USA, Concord, CA, U.S.A.) 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 each day from a concentrate and was placed in a large reservoir (approximately 80 L). Urea and creatinine (Sigma Chemical, St. Louis, MO, U.S.A.) were then added to the blood reservoir such that the urea nitrogen and creatinine concentrations were approximately 90 and 15 mg/dL, respectively. The solution in the reservoir was continuously recirculated and heated to maintain the temperature at 37°C. The solution for the dialysate flow pathway was generated continuously from concentrate by the dialysis delivery system during the experiment and was identical in composition to that in the blood flow pathway except that it was devoid of urea and creatinine. The solutions for both pathways circulated separately in single pass, countercurrent fashion.

Urea and creatinine clearances were determined at a nominal blood flow rate of 300 mL/min and several different dialysate flow rates: 300, 500, and 800 mL/min for both the F5 and F8 dialyzers. Additional experiments were performed with the F5 dialyzers at dialysate flow rates of 100 and 300 mL/min using a separate peristaltic pump to circulate fluid in the dialysate compartment, since very low dialysate flow rates could not be achieved using the 2008E dialysis delivery system. The experiments using the alternative pump at a flow rate of 300 mL/min were performed to test for differences when using either the 2008E dialysis delivery system or the alternative pump to control dialysate flow. Experiments were not performed at 100 mL/min for the F8 dialyzer, since these conditions were not expected during any current clinical hemodialysis strategy. Clearance determinations were performed at different dialysate flow rates in random order, and the net 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 timed collections of the outflow from the respective pathways. Samples for clearance determinations were obtained using needles and syringes in rapid succession from the dialysate outlet, venous tubing, and arterial tubing (in that order) three separate times for each flow condition described above. The samples were kept at 4°C and assayed within 28 hours for urea nitrogen and creatinine.

Analytical

The concentrations of urea nitrogen and creatinine in all samples were determined by automated assays (CX7, Beckman, Fullerton, CA, U.S.A.).

Data analyses

Both blood side and dialysate side solute clearances were calculated using standard formulas [2]. 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 concentration in the blood inlet (arterial), C_{bo} denotes the concentration in the blood outlet (venous), and C_{do} denotes the concentration in the dialysate outlet.

Solute K_oA values were calculated from the mean of the blood and dialysate side clearances (K_d) using the following equation for countercurrent blood and dialysate flows [9]:

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

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

Statistics

Six F5 and three F8 dialyzers were studied; variability between the tested dialyzers was expressed as the standard deviation (SD). Comparison of solute K_oA values between the different dialysate flow rates was performed using analysis of variance (ANOVA) with repeated measures [10].

Results

Measured blood and dialysate flow rates approximated the nominal values. Mass balance errors in all experiments were uniformly small (<5%) except for the F5 dialyzers at a dialysate flow rate of 100 mL/min where they averaged –19% and –24% for urea and creatinine, respectively. There is no ready explanation for solute clearances to be higher on the dialysate than on the blood side at this low dialysate flow rate. Urea and creatinine clearances at a dialysate flow rate of 300 mL/min for the F5 dialyzer were similar for both methods of controlling the dialysate flow rate; these data were averaged together.

The dependences of urea and creatinine K_oA values on the dialysate flow rate for F5 and F8 dialyzers are shown in Tables I and II, respectively. Differences were established by ANOVA in the urea and creatinine K_oA values between the different dialysate flow rates for the F5 dialyzers ($p < 0.001$ and $p < 0.0001$, respectively). The effect of dialysate flow rate on urea and creatinine K_oA values for the F8 dialyzers was similar ($p = 0.01$ and $p < 0.01$, respectively). The individual urea and creatinine K_oA values for the F5 dialyzer are plotted as a function of the measured dialysate flow rate in Fig. 1. The slope of the increase in urea and creatinine K_oA values with increasing dialysate flow rate was significantly different from zero ($p < 0.0001$) and was virtually identical for both solutes when expressed as a percentage of the K_oA value at a dialysate flow rate of 500 mL/min (6% increase in K_oA per 100 mL/min increase in dialysate flow rate). Results for the F8 dialyzer are shown in Fig. 2. The slope of the increase in urea and creatinine K_oA values with increasing dialysate flow rate was different from zero ($p < 0.01$) and was also virtually identical for both solutes when expressed as a percentage of the K_oA value at a dialysate flow rate of 500 mL/min (10% increase in K_oA per 100 mL/min increase in dialysate flow rate).

Discussion

The dialyzer K_oA value characterizes the permeability of the mass transfer barrier between the blood and dialysate pathways of a hemodialyzer. Increasing the dialysate flow rate likely decreases the thickness of the stagnant fluid layer

TABLE I Urea and creatinine mass transfer area coefficients (K_oA) for F5 dialyzers (N = 6). Mean values±SD are reported.

Nominal dialysate flow rate (mL/min)	*Urea K_oA (mL/min)*	*Creatinine K_oA (mL/min)*
800	450±30	310±20
500	410±40	290±30
300	360±20	250±10
100	270±110	190±50

TABLE II Urea and creatinine mass transfer area coefficients (K_oA) for F8 dialyzers (N = 3). Mean values±SD are reported.

Nominal dialysate flow rate (mL/min)	*Urea K_oA (mL/min)*	*Creatinine K_oA (mL/min)*
800	690±20	520±20
500	560±80	420±50
300	420±140	320±100

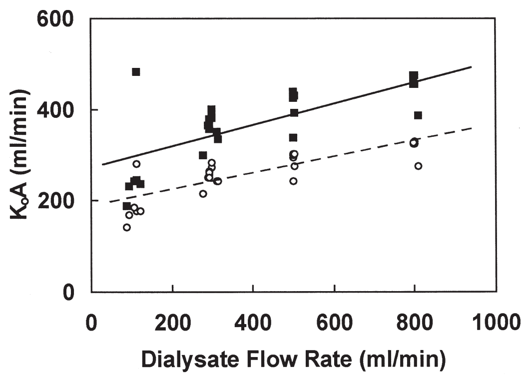

FIGURE 1 Individual mass transfer area coefficients (K_oA) for urea (filled squares) and creatinine (open circles) for the F5 dialyzer plotted versus the measured dialysate flow rate. The solid line shows the best fit linear regression line for the urea data ($Y = 0.250 \times X + 270$), and the dashed line shows the best fit linear regression line for the creatinine data ($Y = 0.170 \times X + 190$).

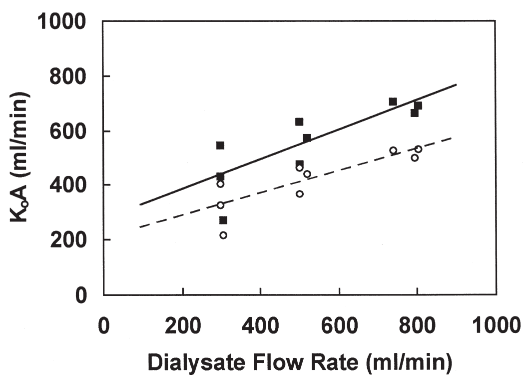

FIGURE 2 Individual mass transfer area coefficients (K_oA) for urea (filled squares) and creatinine (open circles) for the F8 dialyzer plotted versus the measured dialysate flow rate. The solid line shows the best fit linear regression line for the urea data ($Y = 0.560 \times X + 260$), and the dashed line shows the best fit linear regression line for the creatinine data ($Y = 0.420 \times X + 200$).

adjacent to the membrane surface [11] and improves the distribution of flow in the dialysate compartment [12]. The former phenomenon would act to increase the mass transfer coefficient (K_o), and the importance of this effect would be more significant for small solutes. The latter phenomenon would act to more equally distribute flow around the outside of the hollow fibers and could result in a larger effective membrane surface area (A); this effect would be independent of solute size. The results of this study show that the percent increase in urea and creatinine K_oA values upon increasing the dialysate flow rate is similar, suggesting that an increase in dialysate flow rate improves the distribution of flow within the dialysate compartment and increases effective membrane surface area.

Table III compares predicted urea clearances for the F5 dialyzer at low dialysate flow rates assuming a constant urea K_oA value with those assuming a urea K_oA value that decreases by 6% for each 100 mL/min decrease in dialysate flow rate. The calculated urea clearances assuming a decreasing urea K_oA value are 5.5% at Q_d of 300 mL/min and 7.6% at Q_d of 100 mL/min lower than those values calculated assuming a constant urea K_oA value. Figure 3 shows the predicted decrease in clearance assuming a decreasing K_oA value for three solutes with different K_oA values. The solute K_oA values were chosen to correspond to urea, creatinine, and a low molecular weight protein such as β_2-microglobulin for a high flux dialyzer [13]. In these calculations it was further assumed that the decrease in solute K_oA was proportional to the solute K_oA value at a dialysate flow rate of 500 mL/min. The calculated results in this figure show that the effect of a decreasing K_oA value when predicting solute clearances is more significant for larger solutes. This is expected, since the clearance for larger solutes is more dependent on effective membrane surface area. It should be emphasized, however, that the clearances calculated for β_2-microglobulin in Fig. 3 are speculative and have not been verified experimentally. Additional studies both *in vitro* and *ex vivo* of clearances for low molecular weight proteins when using high flux dialyzers are necessary to test these predictions.

The results of the current study confirm and extend previous work [3] showing that changes in dialysate flow rate

TABLE III Calculated urea clearances (K_d) at low dialysate flow rates (Q_d) for the F5 dialyzer

Q_d (mL/min)	K_d with Constant K_oA (mL/min)	K_d with varying K_oA (mL/min)	Percent decrease in K_d with varying K_oA
500	193.6	193.6	—
300	173.2	163.6	5.5
100	95.6	88.3	7.6

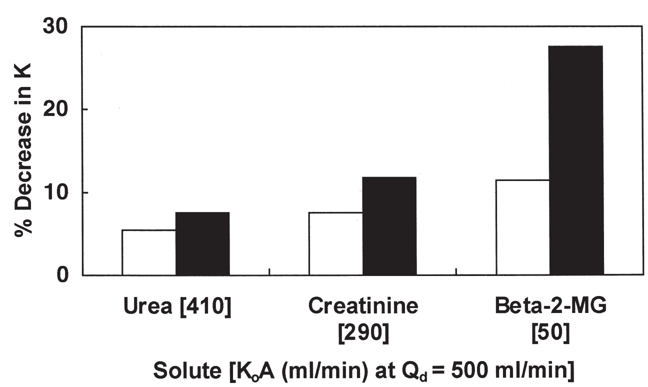

FIGURE 3 The calculated percent decrease in clearance (K) at a dialysate flow rate (Q_d) of 300 mL/min (white bars) and 100 mL/min (black bars) for varying solute mass transfer area coefficients (K_oA) compared with that for constant solute K_oA for three solutes with different K_oA at Q_d of 500 mL/min for a hypothetical high flux dialyzer.

can alter K_oA values for both urea and creatinine. The extent to which these *in vitro* observations occur during clinical hemodialysis remains to be demonstrated.

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