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Original Articles

Multipass haemodialysis: a novel dialysis modality

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ABSTRACT

Introduction. Most home haemodialysis (HD) modalities are limited to home use since they are based on a single-pass (SP) technique, which requires preparation of large amounts of dialysate. We present a new dialysis method, which requires minimal dialysate volumes, continuously recycled during treatment [multipass HD (MPHD)]. Theoretical calculations suggest that MPHD performed six times weekly for 8 h/night, using a dialysate bath containing 50% of the calculated body water, will achieve urea clearances equivalent to conventional HD 4 h thrice weekly, and a substantial clearance of higher middle molecules.

Methods. Ten stable HD patients were dialyzed for 4 h using standard SPHD (dialysate flow 500 mL/min). Used dialysate was collected. One week later, an 8-h MPHD was performed. The dialysate volume was 50% of the calculated water volume, the dialysate inflow 500 mL/min−0.5 × ultrafiltration/min and the outflow 500 mL/min + 0.5 × ultrafiltration/min. Elimination rates of urea, creatinine, uric acid, phosphate and β2-microglobulin (B2M) and dialysate saturation were determined hourly.

Results. Three hours of MPHD removed 49, 54, 50, 51 and 57%, respectively, of the amounts of urea, creatinine, uric acid, phosphate and B2M that were removed by 4 h conventional HD. The corresponding figures after 8 h MPHD were 63, 78, 74, 78 and 111%.

Conclusions. Clearance of small molecules using MPHD 6 × 8 h/week will exceed traditional HD 3 × 4 h/week. Similarly, clearance of large molecules will significantly exceed traditional HD and HD 5 × 2.5 h/week. This modality will increase patients' freedom of movement compared with traditional home HD. The new method can also be used in the intensive care unit and for automated peritoneal dialysis.

INTRODUCTION

Hospital haemodialysis (HD) treatment is usually performed for 4 h thrice weekly. Increasing dialysis frequency and duration has a number of positive effects. Studies show better blood pressure control, cognitive and sexual function and reduced anaemia, myocardial stunning, left ventricular hypertrophy and sleep apnoea [1–9]. Home HD may offer survival rates similar to cadaver renal transplantation [10]. It usually uses the same setup as in-centre HD; however, home HD training is relatively difficult. Even dedicated home HD departments typically have a training period of 5–6 weeks [11]. Access to a good quality water supply is necessary and substantial plumbing and electrical alterations to the home are required. Dialysate consumption is high, usually 500 mL/min. Dialysis machines take up a lot of space and can be difficult to use [12]. Even practiced home HD patients use up to 1.5 h per session for preparation before, and cleaning up after, each session [13].

A recent system, NxStage One, is easy to use, and does not need prior home changes. NxStage HD 3 × 6 h/week results in urea, phosphate and β2-microglobulin (B2M) clearances equivalent to conventional HD 3 × 4 h/week [14]. NxStage One is a single-pass (SP) batch system, where the dialysate passes through the dialysis filter only once.

We have previously demonstrated in an *in vitro* model that dialysate recirculation [multipass HD (MPHD)] results in a significantly increased elimination of urea and creatinine compared with SP dialysis using the same dialysate volume [15]. The purpose of this study was to investigate the effect *in vivo*

of MPHD using a limited volume of dialysate. Theoretical considerations show that MPHD 6 × 8 h/week will result in a small molecular clearance at least as high as conventional single pass HD (SPHD) 3 × 4 h/week and that large molecular clearance will be substantially greater.

MATERIALS AND METHODS

Patients

Ten stable HD patients, all receiving standard in-centre HD three times per week, were included in this study. Exclusion criteria were: age <18 years, psychiatric disease, ultrafiltration requirement >4 L per session, possibility for pregnancy and severe comorbidity. All patients gave informed consent according to the Helsinki II declaration. The protocol was approved by the local ethics committee (identification number H-2-2009-082) and registered in ClinicalTrials.gov (identification number NCT01267760). The trial was controlled by the local Good Clinical Practice unit. Prior to the study, catheter/fistula recirculation was excluded using the indicator dilution technique and the Krivitski method (HD 01 plus, Transonic Systems, Ithaca, NY). All patients used the Polyflux H filter (Gambro, Lund, Sweden), either 170H (three patients) or 210H. These filters have a surface area of 1.7 and 2.1 m^2, respectively. Total body water (TBW_{bio}) was measured using multifrequency bioimpedance (Body Composition Monitor, Fresenius), but this figure was not used in dialysate prescription.

Design

Each patient was studied twice with a 1-week interval. The first treatment was a standard SPHD lasting 4 h, with a dialysate flow of 500 mL/min. The dialysate was continuously collected in a chamber placed upon electronic scales. A blender was placed in the chamber to ensure adequate mixing, such that all samples were representative. The second treatment (MPHD) used a purpose-built functional model. The principle is illustrated in Figure 1. The dialysate chamber (called 'container' in the figure) contained standard dialysate. The standard dialysate was prepared by a dialysis machine (AK-200, Gambro) and was therefore identical, in both treatments. Two pumps controlled dialysate inflow and outflow, and the ultrafiltration. The dialysate was returned to the chamber and thus recirculated. The dialysate circuit was closed and consisted of a dialysate container, two dialysate tubes and a dialysis filter. The chamber was placed on electronic scales, and a seesaw mechanism was applied to assure optimal mixing. The dialysate temperature was continuously registered. A heater element (not shown) kept the dialysis filter inflow temperature between 36 and 37°C. In addition, the model was equipped with all the usual elements: blood pump, pressure sensors, air detector etc. The dialysate inflow was 500 mL/min − (1/2 × ultrafiltration/min) and outflow 500 mL/min + (1/2 × ultrafiltration/min). The difference determines the ultrafiltration rate. The chamber weight was used as an extra control, and the model was controlled by a pre-programmed PC. The dialysate volume was individual, corresponding to 50% of the patient's calculated TBW. TBW was estimated as 55% of female dry weight and 60% of male (TBW_{calc}). One patient, with a body weight of 111 kg and an estimated TBW of 66 kg, was treated with only 30.4 L of dialysate due to the size of the dialysate chamber.

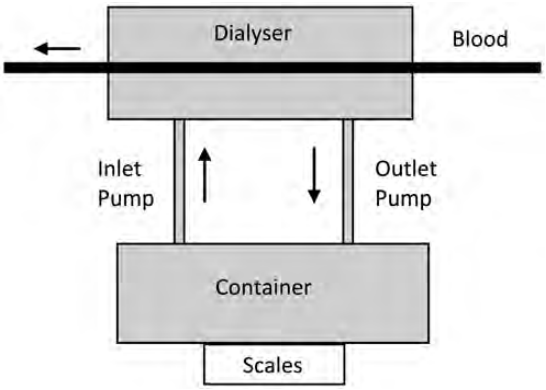

FIGURE 1: Schematic representation of the MPHD model. The black arrow shows the blood flow through the dialysis filter. The dialysate is kept in the container. It is pumped into the filter using an inflow pump (P-I) and out of the filter using an outflow pump (P-O). The difference in pump flow rates determines the ultrafiltration. The combined weight of dialysate and ultrafiltrate is registered continuously by the scales.

Anticoagulation was performed using fractionated heparin. The patient's usual dose was used for SPHD and at the start of MPHD. After 4 h MPHD, a new bolus was given.

Monitoring and investigations

Blood pressure was measured every hour. After 0, 2, 4 and 8 h, patients reported a visual analogue score on a scale of 0–10 for the following symptoms: fatigue, nausea, muscle cramps, concentration difficulty, general malaise and headache. Arterial blood was drawn at the start.

The following were registered at hourly intervals: dialysate consumption, ultrafiltration and blood pressure. Dialysate, arterial and venous blood samples were drawn every hour and stored at −80°C until analysis.

The dialysate samples, which were taken every hour from the filter inflow, were continuously monitored visually for any cloudiness that might represent precipitation. All dialysate was subsequently centrifuged at 3000 rpm for 10 min, and then investigated visually for precipitation.

Markers and calculations

Urea, creatinine, uric acid and phosphate were used as markers for small molecules and B2M for middle molecules. Urea, creatinine, uric acid and phosphate were determined using the Vitros analyser (Ortho Clinical Diagnostics, Johnson & Johnson, Rochester) and B2M using the Immulite immunoassay (Siemens, Erlanger, Germany).

First, the effect of dialysis for both SPHD and MPHD is expressed as the amount of toxin found in used dialysate plus ultrafiltrate, calculated hourly:

$$\text{Removed toxin} = C_{\text{toxin}} \times \text{Vol}_{\text{dialysate}} + \text{ultrafiltrate}$$

Secondly, MPHD dialysate is gradually saturated with toxin. The amount of unsaturated dialysate pumped into the filter per

minute at time t is calculated thus: if D is the dialysate toxin concentration at time t and A the arterial concentration, then the fraction of unsaturated dialysate at time t is $(1 - D/A)$. The ultrafiltration was an average of 6 mL/min. Since the inflow pump operated at a speed of 500–0.5 × ultrafiltration mL/min, the amount of unsaturated dialysate pumped into the filter at time t was $(500 - 0.5 \times 6)(1 - D/A) = 497 \times (1 - D/A)$.

Urea kinetics

Urea kinetics were determined both as calculated (calc) and measured (meas) values.

Calculated Kt/V

Overhydration at time t (OH_t) was defined as:

$$\text{Dialysis A}: \quad OH_t = \frac{DV_t - 30 \times t}{DTBW_{calc}}$$

$$\text{Dialysis B}: \quad OH_t = \frac{DV_t - DV_o}{DTBW_{calc}}$$

Single-pool Kt/V (spKt/V) at time t, measured in hours for urea, was determined using the Daugirdas formula [16].

$$R = ABC_t / ABC_0$$

$$spKt/V_t = -\log_n(R - 0.008 \times t) + (4 - 3.5 \times R) \times OH_t / DTBW_{calc}$$

Standard Kt/V (stdKt/V) is an adjustment of spKt/V to take into account the fact that discontinuous dialysis therapies are less effective than continuous. StdKt/V is equivalent weekly Kt/V for a continuous therapy. Thus, stdKt/V < (spKt/V × number of dialyses per week).

The two values will be closer to each other if the number of weekly dialyses is six (stdKt/V_6) rather than three (stdKt/V_3), and if the spKt/V is low. The method of Gotch [17] was used to measure stdKt/V, using simplified derived formulae:

$$\text{Dialysis} \times 3/\text{week}: \quad stdKt/V = 3.354 - e^{(1.21 - 0.735 spKt/V)}$$

$$\text{Dialysis} \times 6/\text{week}: \quad stdKt/V = 6.754 - e^{(1.91 - 0.769 spKt/V)}$$

Measured Kt/V

The fraction of removed substance in the dialysate, F_{dial}, at time t was defined as:

$$F_{dial} = \frac{DV_t \times DC_t}{ABC_o \times (OH_o + DTB_{bio})}$$

$$Clearance_{dial} = ((F_{dial} \text{ at time } t) - (F_{dial} \text{ at time } t - 1)) \times ((TBW_{bio} \text{ at time } t) + (TBW_{bio} \text{ at time } t - 1))/2$$

For urea:

$$spKt/V = -\log_n(F_{dial} - 0.008 \times t)$$

Fractional clearance (FC_{blood}) and blood clearance ($Clearance_{blood}$) at time t were determined from the pre-filter (arterial) and post-filter (venous) blood concentrations, and the blood flow (BF):

$$\text{Fractional clearance}_{blood} = 1 - \frac{BVC_t \times (BF - \text{ultrafiltration rate in mL/min})}{ABC_t \times BF}$$

$$Clearance_{blood} = BF \times FC_{blood}$$

Since dialysate concentration in multipass dialysis will always be >0, clearance will be lower than with SP dialysis. To compare filter performance, relative fractional clearance (RFC_{blood}) and relative blood clearance were defined as the clearance relative to the difference between arterial blood and dialysate concentrations:

$$RFC_{blood} = \frac{BF \times (1 - (BVC_t) \times (BF - \text{ultrafiltration rate in mL/min})}{(ABC_t - DC_t) \times BF}$$

$$\text{Relative clearance}_{blood} = BF \times RFC_{blood}$$

Statistics

Variables were compared using Student's t-test. Correlation analysis was performed using Pearson's product–moment analysis. Significance was determined as $P < 0.05$. The software used was Statistica 10.0 (StatSoft, Tulsa, OK).

RESULTS

The patient age was 63.1 ± 11.7 years. Three were women. The dialysis vintage was 6.5 ± 4.4 years. Renal diagnoses were hypertensive nephropathy 3, polycystic renal disease 2, glomerulonephritis 1, chronic interstitial nephropathy 1 and unknown 3. Six patients had a diuresis >300 mL/day. Their creatinine clearance was 4.4 ± 2.6 mL/min. The dry weight was 79.2 ± 18.4 kg. The calculated TBW was 46.3 ± 10.6 kg. MPHD dialysate volume was 22.9 ± 4.8 L (range 13.8–30.4).

The initial SPHD s-urea was 19.5 ± 7.3 mmol/L versus MPHD 20.5 ± 7.6 mmol/L (not significant, NS). The corresponding figures for s-creatinine were 723 ± 220 versus 743 ± 204 µmol/L (NS), s-uric acid 0.32 ± 0.13 versus 0.31 ± 0.07 (NS), serum phosphate (s-phosphate)1.59 ± 0.53 versus 1.48 ± 0.34 mmol/L (NS) and s-B2M 1858 ± 647 nmol/L versus 1746 ± 565 nmol/L (NS). S-phosphate fell to 0.89 ± 0.17 mmol/L after 3 h SPHD, and did not change during the last hour. During MPHD, it fell to 0.99 ± 0.17 after 3 h, and then gradually rose to 1.17 ± 0.14 mmol/L. The initial blood pressure was: for SPHD 147 ± 19/77 ± 10 and for MPHD 140 ± 23/75 ± 19 mmHg (NS) and the final blood pressure was 132 ± 15/73 ± 9 and 131 ± 14/73 ± 10 mmHg (NS). SPHD blood flow was 276 ± 40 mL/min and MPHD blood flow was 279 ± 42 mL/min (NS). The total ultrafiltration during SPHD was 2.28 ± 1.05 and during MPHD 2.57 ± 1.32 L (NS). The maximal ultrafiltration was 4 L in both treatments. Two patients required therapeutic intervention during the treatment, one for hypotension and one for muscle cramps. Both problems occurred during SPHD. Other side effects were clinically insignificant. No dialysate cloudiness suggestive of precipitation was seen at any time, and no precipitation was

seen after centrifugation. There were no episodes of filter coagulation.

Figure 2 shows the effects of MPHD. Urea, creatinine, uric acid and phosphate removal during 4 h SPHD was 510 ± 172, 14.45 ± 5.19, 5.27 ± 1.45 and 31.34 ± 8.59 mmol, respectively, and B2M removal was 12.69 ± 4.74 µmol. Toxin elimination is compared with these figures, indexed with a value of 1. After 3 h MPHD, urea, creatinine, uric acid, phosphate and B2M removal corresponded to 49, 54, 50, 51 and 57% of the value achieved by 4 h SPHD. After 8 h treatment the figures rose to 63, 78, 74, 78 and 111%. The amount of toxin removed during the last 5 h MPHD corresponded to 22, 31, 32, 35 and 49% of the total MPHD removal, respectively.

Figure 3 shows the amount of unsaturated dialysate passing the dialysis filter per minute during MPHD. The amount of unsaturated dialysate passing through the filter after 8 h MPHD was 30–94 mL/min for small molecules and 219 mL/min for B2M. Table 1 shows urea, creatinine, uric acid, phosphate and B2M dialysate concentrations after the two treatments. Table 2 shows the calculated amount of toxin removed per week using conventional SPHD compared with 8 h MPHD for five and six times per week. Tables 3 and 4 show the results of the clearance and kinetic measurements.

The calculated TBW was 46.3 ± 10.6 L and the TBW as determined by bioimpedance was 39.3 ± 4.5 L. The difference was significantly related to body weight, being greatest in heavy patients (Figure 4).

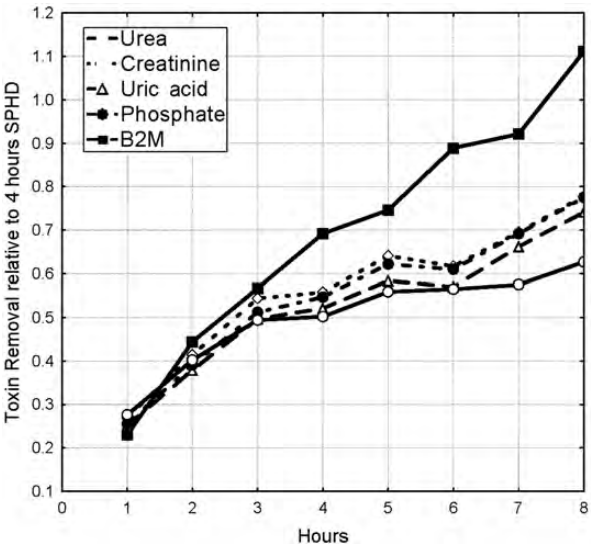

FIGURE 2: Removal of urea, creatinine, uric acid, phosphate and B2M in dialysate and ultrafiltration as a function of time, compared with the amount removed after 4 h SPHD.

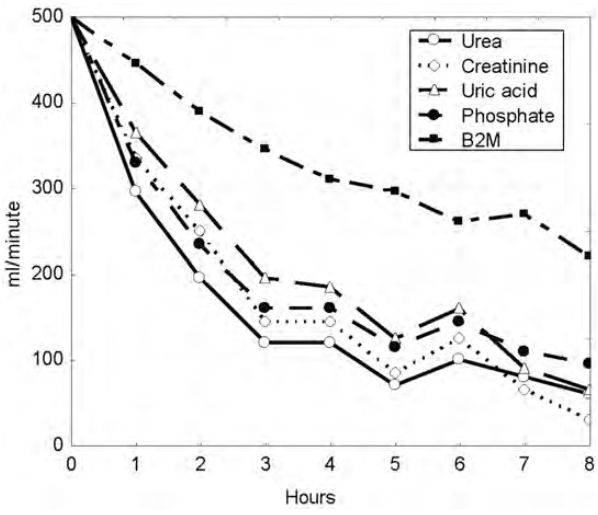

FIGURE 3: Toxin-free dialysate flow as a function of time.

DISCUSSION

Dialysate recirculation using at tank/batch system has been known for many years, indeed since the infancy of maintenance dialysis. For instance, Schribner *et al.* described in 1960 a 360-L tank system [18]. The system was of course intended for use as an in-centre treatment with nursing supervision. Buoncristiani *et al.* have described a batch system designed for home use. It consisted of a daily 90-min treatment using 20–25 L of dialysate recirculating at 1400 mL/min [19]. The treatment results of seven patients were described as good. The present system differs from previous recirculation systems in that it uses an individualized minimal dialysate volume for an 8-h treatment. We chose a dialysate volume of one half of estimated TBW in that complete saturation will result in a urea Kt/V of 0.33 per treatment, which is adequate. The choice of a dialysate flow of 500 mL/min was arbitrary. The small dialysate volume, similar to volumes used in automated peritoneal dialysis, permits delivery of pre-prepared dialysate to the patient's own home or travel destination. After only 3 h of dialysis, MPHD removed one half of the amount of urea, creatinine, uric acid and phosphate removed by 4 h SPHD. Thus, MPHD 6 × 3 h/week will achieve at least the same urea, creatinine, uric acid and phosphate elimination as conventional in-

Table 1. Amounts of removed toxins per litre used dialysate + ultrafiltrate

	SPHD 4 h	MPHD 8 h	MPHD/SPHD ratio
Urea (mmol/L)	4.2 ± 1.4	12.6 ± 4.5	3
Creatinine (µmol/L)	118 ± 42	436 ± 119	3.7
Uric acid (mmol/L)	0.04 ± 0.01	0.16 ± 0.04	4
Phosphate (mmol/L)	0.26 ± 0.07	0.96 ± 0.12	3.7
B2M (nmol/L)	104 ± 38	558 ± 213	5.4

Table 2. Amount of removed toxin using SPHD 4 h three times per week compared with MPHD 8 h five and six times per week

	SP 4 h ×3/week	MPHD 8 h ×5/week	Significance	MPHD 8 h ×6/week	Significance
Urea, mmol/week	1531 ± 517	1580 ± 654	NS	1895 ± 785	0.03
Creatinine, mmol/week	43.4 ± 15.6	55.4 ± 23.1	0.01	66.4 ± 27.7	0.007
Uric acid, mmol/week	15.8 ± 4.4	19.3 ± 5.7	0.02	23.1 ± 6.8	0.007
Phosphate, mmol/week	94.0 ± 25.8	120.0 ± 26.3	0.02	143.9 ± 31.6	0.009
B2M, µmol/week	38.1 ± 14.2	70.5 ± 30.0	0.005	84.6 ± 36.1	0.005

Table 3. Urea kinetics. A: 4 hour SPHD; B: 8 hour MPHD

Urea	Dialysis	Calculated			Measured		
		3 h	4 h	8 h	3 h	4 h	8 h
spKt/V	A	1.04 ± 0.27	1.42 ± 0.39		0.88 ± 0.16	1.28 ± 0.22	
	B	0.47 ± 0.08	0.48 ± 0.09	0.56 ± 0.12	0.41 ± 0.07	0.43 ± 0.08	0.63 ± 0.10
stdKt/V (×3/week)	A	1.76 ± 0.31	2.13 ± 0.35		1.58 ± 0.20	2.03 ± 0.21	
	B	0.97 ± 0.15	1.00 ± 0.17	1.13 ± 0.20	0.87 ± 0.12	0.90 ± 0.14	1.23 ± 0.15
stdKt/V (×6/week)	A	3.66 ± 0.64	4.39 ± 0.70		3.29 ± 0.41	4.20 ± 0.43	
	B	2.03 ± 0.30	2.09 ± 0.35	2.36 ± 0.41	1.81 ± 0.25	1.89 ± 0.30	2.57 ± 0.30
Meas/calc ratio	A				0.93 ± 0.23	0.98 ± 0.20	
	B				0.91 ± 0.18	0.93 ± 0.24	1.14 ± 0.37

centre HD therapy. The results presented here underestimate the achievable results using MPHD, since we designed the system to perform full mixing of the dialysate right from the start. In a system where only clean dialysate is initially used, some 40 min would pass before recycled dialysate was used, and MPHD would achieve identical results to SPHD during this period. This initial advantage would however probably be rapidly attenuated thereafter.

It would however be a mistake to interrupt MPHD after 3 h. Longer treatment times will preferentially increase the removal of large molecules. In one study [20], an increase in dialysis time from 4 to 8 h using the same dialysate volume resulted in increases in the removal of urea, creatinine, phosphate and B2M by 26.1, 35.5, 48.9 and 81.2%, respectively. Thus, the larger the molecule, the greater the resistance to dialysis, and the greater the effect of longer dialysis. The cell wall offers greatest resistance to diffusion for intracellular molecules [21].

Phosphate elimination is special. With more frequent dialysis, there are increased intradialytic s-phosphate concentrations during the first hour, and this will increase the phosphate removal substantially. S-phosphate fell to minimum values after 3 h of both SPHD and MPHD. The concentration rose thereafter during MPHD from 0.99 to 1.17 mmol/L, probably due to mobilization of phosphate from the deep compartments. A rising concentration during dialysis is an advantage, since clearance will rise correspondingly. The present paper can be compared with the study by Mucsi *et al.* [22]. Here, patients were switched from conventional HD to nocturnal HD (NHD) 8 h 6–7/week. Conventional HD removed 25.3 ± 7.5 mmol per treatment, whereas NHD removed 26.9 ± 9.8. In our study, MPHD removed 24.0 ± 4.5 mmol. This result is comparable with Mucsi's results, despite the fact that pre-dialysis s-phosphate was 1.48 mmol/L compared with 2.1 in Mucsi's study. It is therefore reasonable to conclude that phosphate control in MPHD will be

Table 4. Clearances

		F_{dial}	$Clearance_{dial}$	Relative clearance[a]	Relative fractional clearance[a]	$Clearance_{blood}$	Fractional clearance	Dialysate Saturation (%)
Urea								
A	1	0.23 ± 0.03	160 ± 19	244 ± 26	0.90 ± 0.05	244 ± 26	0.90 ± 0.05	
	2	0.39 ± 0.06	110 ± 33	247 ± 26	0.90 ± 0.04	247 ± 26	0.90 ± 0.04	
	3	0.62 ± 0.22	117 ± 54	245 ± 29	0.89 ± 0.04	245 ± 29	0.89 ± 0.04	
	4	0.68 ± 0.06	103 ± 64	240 ± 32	0.87 ± 0.04	240 ± 32	0.87 ± 0.04	
B	1	0.18 ± 0.03	122 ± 19	224 ± 27	0.82 ± 0.09	131 ± 22	0.48 ± 0.09	41
	2	0.25 ± 0.04	54 ± 32	179 ± 73	0.66 ± 0.27	70 ± 29	0.26 ± 0.12	61
	3	0.31 ± 0.04	40 ± 16	155 ± 69	0.57 ± 0.27	36 ± 17	0.14 ± 0.07	76
	4	0.31 ± 0.05	4 ± 22	126 ± 78	0.46 ± 0.28	25 ± 13	0.09 ± 0.06	76
	5	0.34 ± 0.07	23 ± 35	85 ± 101	0.35 ± 0.42	10 ± 10	0.04 ± 0.04	86
	6	0.35 ± 0.09	5 ± 27	49 ± 62	0.19 ± 0.23	13 ± 19	0.05 ± 0.06	80
	7	0.36 ± 0.06	20 ± 26	72 ± 86	0.26 ± 0.32	8 ± 8	0.03 ± 0.03	84
	8	0.40 ± 0.05	26 ± 37	114 ± 113	0.42 ± 0.38	9 ± 10	0.03 ± 0.04	88
Creatinine								
A	1	0.16 ± 0.01	113 ± 16	200 ± 29	0.73 ± 0.06	200 ± 29	0.73 ± 0.06	
	2	0.28 ± 0.05	82 ± 27	198 ± 22	0.72 ± 0.06	198 ± 22	0.72 ± 0.06	
	3	0.41 ± 0.07	86 ± 40	196 ± 27	0.71 ± 0.06	196 ± 26	0.71 ± 0.06	
	4	0.51 ± 0.08	69 ± 26	219 ± 39	0.79 ± 0.08	219 ± 39	0.79 ± 0.08	
B	1	0.13 ± 0.02	93 ± 16	195 ± 23	0.71 ± 0.07	131 ± 20	0.48 ± 0.08	32
	2	0.20 ± 0.03	48 ± 27	188 ± 40	0.68 ± 0.14	93 ± 19	0.34 ± 0.09	50
	3	0.26 ± 0.04	43 ± 14	194 ± 70	0.70 ± 0.24	54 ± 20	0.20 ± 0.09	71
	4	0.27 ± 0.04	6 ± 21	158 ± 68	0.59 ± 0.30	42 ± 18	0.16 ± 0.09	71
	5	0.31 ± 0.06	26 ± 37	149 ± 124	0.54 ± 0.42	18 ± 16	0.07 ± 0.07	83
	6	0.30 ± 0.08	-9 ± 20	146 ± 108	0.53 ± 0.37	31 ± 25	0.12 ± 0.09	74
	7	0.34 ± 0.06	28 ± 29	154 ± 98	0.58 ± 0.36	19 ± 12	0.07 ± 0.05	87
	8	0.38 ± 0.05	26 ± 41	173 ± 118	0.64 ± 0.41	26 ± 42	0.09 ± 0.13	94

Urate								
A	1	0.14 ± 0.01	98 ± 14	201 ± 25	0.74 ± 0.05	201 ± 25	0.74 ± 0.05	
	2	0.24 ± 0.05	67 ± 27	192 ± 24	0.70 ± 0.08	192 ± 24	0.70 ± 0.08	
	3	0.34 ± 0.07	67 ± 44	190 ± 20	0.69 ± 0.06	190 ± 20	0.69 ± 0.06	
	4	0.43 ± 0.08	62 ± 21	167 ± 44	0.62 ± 0.17	167 ± 44	0.62 ± 0.17	
B	1	0.11 ± 0.02	75 ± 17	181 ± 26	0.66 ± 0.08	132 ± 20	0.49 ± 0.08	27
	2	0.16 ± 0.03	38 ± 21	157 ± 45	0.57 ± 0.17	86 ± 24	0.32 ± 0.10	44
	3	0.21 ± 0.04	34 ± 15	138 ± 47	0.50 ± 0.18	52 ± 20	0.19 ± 0.09	61
	4	0.22 ± 0.05	4 ± 18	103 ± 65	0.39 ± 0.27	34 ± 23	0.13 ± 0.11	63
	5	0.25 ± 0.06	22 ± 27	61 ± 53	0.24 ± 0.22	16 ± 14	0.06 ± 0.06	75
	6	0.24 ± 0.07	-4 ± 22	93 ± 71	0.35 ± 0.25	28 ± 24	0.10 ± 0.08	68
	7	0.28 ± 0.06	27 ± 24	105 ± 79	0.39 ± 0.28	15 ± 11	0.06 ± 0.04	82
	8	0.32 ± 0.05	22 ± 36	116 ± 99	0.42 ± 0.33	13 ± 15	0.05 ± 0.06	86
Phosphate								
A	1	0.16 ± 0.02	115 ± 19	215 ± 33	0.78 ± 0.03	215 ± 33	0.78 ± 0.03	
	2	0.28 ± 0.05	74 ± 25	218 ± 28	0.79 ± 0.05	218 ± 28	0.79 ± 0.05	
	3	0.40 ± 0.07	88 ± 45	216 ± 27	0.78 ± 0.05	216 ± 27	0.78 ± 0.05	
	4	0.56 ± 0.16	103 ± 90	222 ± 30	0.81 ± 0.03	222 ± 30	0.81 ± 0.03	
B	1	0.14 ± 0.02	97 ± 17	206 ± 27	0.75 ± 0.06	134 ± 18	0.49 ± 0.06	34
	2	0.21 ± 0.04	53 ± 31	192 ± 63	0.70 ± 0.22	90 ± 29	0.33 ± 0.12	53
	3	0.28 ± 0.04	43 ± 13	202 ± 54	0.73 ± 0.19	63 ± 21	0.23 ± 0.09	68
	4	0.29 ± 0.05	12 ± 18	169 ± 64	0.61 ± 0.23	51 ± 17	0.19 ± 0.07	68
	5	0.34 ± 0.07	31 ± 36	150 ± 76	0.56 ± 0.31	33 ± 17	0.12 ± 0.08	77
	6	0.33 ± 0.08	-3 ± 19	140 ± 88	0.51 ± 0.32	37 ± 23	0.14 ± 0.08	71
	7	0.38 ± 0.06	29 ± 20	154 ± 74	0.56 ± 0.27	29 ± 20	0.11 ± 0.07	78
	8	0.43 ± 0.07	32 ± 34	151 ± 81	0.55 ± 0.28	27 ± 17	0.10 ± 0.08	81
β2-Microglobulin								
A	1	0.06 ± 0.01		89 ± 21	0.32 ± 0.07	89 ± 21	0.32 ± 0.07	
	2	0.10 ± 0.01	31 ± 10	80 ± 17	0.29 ± 0.07	80 ± 17	0.29 ± 0.07	
	3	0.15 ± 0.02	31 ± 13	80 ± 23	0.29 ± 0.08	80 ± 23	0.29 ± 0.08	
	4	0.18 ± 0.04	20 ± 11	87 ± 18	0.32 ± 0.07	87 ± 18	0.32 ± 0.07	

Continued

Table 1. Continued

B	1	0.04 ± 0.01		68 ± 18	0.25 ± 0.05	61±16	0.22 ± 0.05	11
	2	0.08 ± 0.02	26 ± 12	70 ± 28	0.25 ± 0.10	54 ± 23	0.20 ± 0.09	22
	3	0.10 ± 0.01	16 ± 13	48 ± 35	0.18 ± 0.13	34 ± 25	0.13 ± 0.09	31
	4	0.13 ± 0.02	15 ± 20	50 ± 37	0.19 ± 0.15	33 ± 25	0.13 .10	38
	5	0.14 ± 0.02	9 ± 24	50 ± 25	0.18 ± 0.09	31 ± 18	0.11 ± 0.07	41
	6	0.16 ± 0.03	15 ± 22	51 ± 41	0.18 ± 0.13	26 ± 20	0.09 ± 0.07	48
	7	0.17 ± 0.04	7 ± 30	75 ± 78	0.28 ± 0.27	27 ± 14	0.10 ± 0.06	46
	8	0.20 ± 0.04	19 ± 22	69 ± 42	0.25 ± 0.13	26 ± 15	0.10 ± 0.06	56

[a]Clearance values less than zero or greater than blood flow were rounded up and down, respectively.

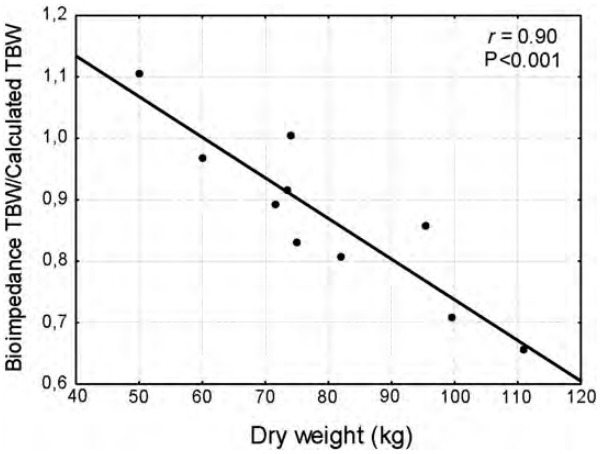

FIGURE 4: Relationship between calculated and measured TBW.

equivalent to NHD, and that the need for phosphate binders will disappear after some months of treatment. A pre-dialysis s-phosphate of 1.3 mmol/L, as achieved by Mucsi after 6 months NHD treatment, is also feasible. The figures for the calculated removal during MHD 5–6/week shown in Table 2 should of course be interpreted with caution. During long-term treatment, body phosphate stores will be depleted, and real phosphate elimination will gradually equilibrate to actual intestinal phosphate absorption. For all solutes, an initial increase in removal will be expected to fall again in the long term, and be replaced by a corresponding fall in pre-dialysis serum concentration.

The situation for B2M is different. B2M is localized to the interstitial environment and plasma. Depending upon the technique used, the distribution volume of B2M is only 14–20% of body weight [23, 24]. The clearance from the interstitial milieu, as determined by post-dilution haemodiafiltration, is 82 ± 7 mL/min and across the dialysis filter 73 ± 2 mL/min [23]. Thus the resistance between the interstitial and plasma compartments is the limiting factor for B2M elimination. In our study, B2M MPHD elimination was 166 ± 71 mg. Raj *et al.* [25] switched 10 chronic HD patients, all treated with high-flux dialysis, to nocturnal dialysis for 6 × 8 h/week. The blood flow was 282 ± 17 and the dialysate flow 99 ± 1 mL/min. The filter area was 0.70 m^2, and an SP technique was used. B2M removal during the first week was 103.0 ± 42.6 mg/treatment. The authors noted that 'in spite of a marked reduction in B2Mpost, the B2Mpost level tends to bounce back to the pre-dialysis value prior to the next dialysis'. The difference between the removed amounts of B2M in our study and Raj *et al.*'s paper is significant. The explanation is partly that Raj *et al.* used a smaller filter, and partly that an SP technique was used with a dialysate flow of only 99 mL/min. S-B2M in Raj *et al.*'s study was 27.2 ± 11.7 mg/L compared with 20.6 ± 6.7 mg/L in the present study. S-B2M fell by half during 9 months of treatment. S-B2M is associated with increased mortality in HD [26, 27]. If this association is causal (which remains to be demonstrated), a reduction in S-B2M could reduce patient mortality.

Table 1 demonstrates that dialysate is utilized better during MPHD than SPHD. The dialysate volumes used in this study (average 22.9 L) may be more than required. While the calculated TBW was 46.3 ± 10.6 L, the TBW as determined by bioimpedance was 39.3 ± 4.5 L, and was relatively lower in heavier

patients (Figure 2). This is intuitively likely, since adipose tissue contains less water. If one assumes that the bioimpedance values are a truer measure of TBW, then these patients will require relatively less dialysate.

There are a number of advantages associated with using a limited dialysate volume in a closed system. Water quality is poor in many parts of the world. Centralized production of dialysate, as already practiced for PD therapy, can ensure the optimal fluid quality. Ultra-pure dialysate results in better preservation of residual renal function and improved nutritional status [28, 29]. Finally, the use of a closed system means that the removal of relevant toxins (e.g. urea, creatinine, uric acid, phosphate and B2M) can be determined exactly, instead of being estimated using the traditional Kt/V methodology.

The dialysis principle presented here is superior to conventional treatment both in regard to small molecules such as urea, creatinine, uric acid, phosphate and even more so as regards large molecules, e.g. B2M. The concept is simple and easily comprehensible. The technical requirements, on top of the normal requirements for a standard dialysis machine (blood pump, pressure sensors, air detector, blood detector etc.), are relatively limited: two pumps and a weighing device. The device would also be simple to use, requiring (i) dialysate installation, (ii) priming, (iii) determination of ultrafiltration, (iv) cannulation, (v) pressing the 'Start' button. The single-use components can be discarded after use. In a recent questionnaire, comprising more than 7000 participants at five international congresses, both patients and nursing staff considered that the main requirements for improved home HD utilization were 'to reduce total time required for dialysis procedures' and 'to simplify and domesticate dialysis procedures' [30]. In a review of problems associated with home HD and nocturnal dialysis in particular, Lockridge and Moran [31] wrote 'the complexity of the conventional dialysis machines and needle disconnection remain the most important clinical obstacles to adoption of NDHD by physicians and patients' and that 'if a dialysis machine is able to deliver long (slow) runs of dialysis safely in the home setting, the authors believe that many more patients would accept and benefit from this optimal form of renal replacement therapy at home'. We suggest that the proposed modality will contribute to these goals.

CONFLICT OF INTEREST STATEMENT

R.S.P. owns shares in Flexdialysis ApS. The results presented in this paper have not been published previously in whole or part, except in abstract format.

(See related article by Vanholder *et al.* Less water for haemodialysis: is multiple pass the future pace to go? *Nephrol Dial Transplant* 2013; 28: 1067–1070.)

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ORIGINAL ARTICLE

Global differences in dialysis modality mix: the role of patient characteristics, macroeconomics and renal service indicators

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