Impact of hemodialysis duration on the removal of uremic retention solutes

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Several studies have stressed the importance of dialysis time in the removal of uremic retention solutes. To further investigate this, nine stable chronic hemodialysis patients were dialyzed for 4, 6, or 8 h processing the same total blood and dialysate volume by the Genius system and high-flux FX80 dialyzers. Inlet blood and outlet dialysate were analyzed for urea, creatinine, phosphorus, and β2-microglobulin at various times. Total solute removal, dialyzer extraction ratios, and total cleared volumes were significantly larger during prolonged dialysis for urea, creatinine, phosphorus, and β2-microglobulin. Reduction ratios increased progressively, except for phosphate and β2-microglobulin, where the ratios remained constant after 2 h. In contrast, no significant difference was found for the reduction ratios of all solutes and Kt/V_{urea} between the three different sessions. With longer dialyses, solutes are efficiently removed from the deeper compartments of the patient's body. Our study shows that care must be taken when using *Kt/V*urea or reduction ratios as the only parameters to quantify dialysis adequacy.

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One of the major aims of renal replacement therapy is to remove uremic waste products. The quantification of this removal is an important parameter in the assessment of adequacy of renal replacement therapy. Urea is currently used as the standard marker for dialysis adequacy, by the calculation of the clearance index Kt/V_{urea} or RR (reduction ratio).[1] Kt/V_{urea} depends, however, on two separately modifiable factors: dialyzer clearance '*K*' and dialysis time '*t*.' As both factors might not have the same impact on solute removal, it is difficult to give a straightforward interpretation to the quantification of Kt/V_{urea}.

Urea kinetics significantly differ from the kinetic behavior of other molecules, such as middle molecules, protein bound solutes, and even other small and water-solutes.[2,3] Several studies stress the importance of time and/or clearance in the removal of difficult-to-remove uremic retention solutes. Dialyzer clearance *K* is a significant contributor to the removal of middle molecules such as β2-microglobulin, at least if pore size is sufficiently large.[4,5] The factor time plays an even more important role in the removal of middle molecules and phosphorus.[3–12] β2-Microglobulin removal is enhanced by increasing dialysis duration,[4–6] whereas phosphorus removal has been linked to dialysis duration[3,7,9,11,12] as well as to dialysis frequency.[8–10] In all these studies, however, the factor time is not the only modified parameter with potential impact on adequacy. In general, in this type of studies, dialysate and blood flows are kept constant, so that it is impossible to assign changes in removal to time only, as prolonging or shortening will result in an increase or decrease of the global blood and dialysate volumes displaced.

The Genius single-pass batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany)[13] uses a double-sided roller pump that generates equal blood and dialysate flows up to 350 ml min^{-1} (Figure 1—point 1). In general, dialysis is ended when the entire volume of dialysate present in this system has crossed the dialyzer. As a consequence, dialysis sessions in spite of markedly different duration still will apply an identical blood and dialysate volume, hence offering the opportunity to evaluate the impact of time as the sole variable. The system consists of a closed dialysate tank of 90 l (Figure 1—point 4) and, although fresh and spent dialysate are stored together,[13–15] dialysis may last up to 10 h when using a blood and dialysate flow of 150 ml min^{-1},

without mixing of fresh and spent dialysate.[16,17] The excess body water that is ultrafiltered out of the patient's plasma is collected in a filtrate recipient (Figure 1—point 3).

In this study, we investigated the isolated effect of the factor time on the removal and kinetic behavior of different molecules such as urea, creatinine, phosphorus, and β2-microglobulin. The same patients were submitted to three different dialysis sessions with the Genius system lasting 4, 6, or 8 h, respectively, whereas blood flow rates were adapted so that the total processed volumes were matched at the end of all sessions.

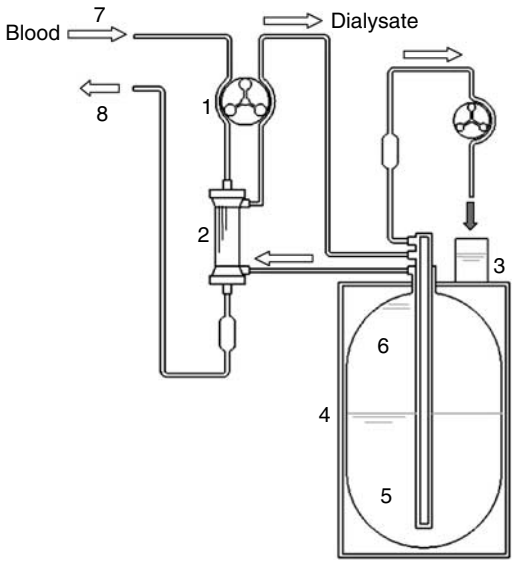

Figure 1 | Flow chart of the Genius dialysis system. (1) Double-sided roller pump, (2) dialyzer, (3) ultrafiltrate recipient, (4) closed container with 90 l dialysate, (5) spent dialysate, (6) fresh dialysate, (7) arterial blood line, and (8) venous blood line.

RESULTS

For the different time schedules, total solute removal (TSR) (panel a), total cleared volume (TCV) (b), dialyzer extraction ratio (c), and reduction ratio (d) are shown in Figure 2 for urea, creatinine, phosphorus, and β2-microglobulin. TSR was significantly larger with protracted dialysis for urea ($P=0.006$), creatinine ($P=0.001$), phosphorus ($P<0.001$), and β2-microglobulin ($P=0.006$) (Figure 2). Paired differences were found between the 4 and 8 h dialysis for all studied solutes ($P=0.008$ for urea, $P<0.001$ for creatinine, and $P=0.004$ for phosphorus and β2-microglobulin), whereas differences between the 4 and 6 h dialysis were found for creatinine ($P=0.001$) and phosphorus ($P=0.008$), and between the 6 and 8 h dialysis for urea ($P=0.008$) and phosphorus ($P=0.027$).

Furthermore, TCV as well as dialyzer extraction ratio, which is a measure for global elimination in the dialyzer irrespective of flow, were significantly higher with a prolonged dialysis session for urea (both $P=0.008$), creatinine (both $P<0.001$), phosphorus (both $P<0.001$), and β2-microglobulin ($P=0.029$ and $P=0.012$) (Figure 2).

No significant differences, however, were found between the different dialysis time schedules for the post-dialysis

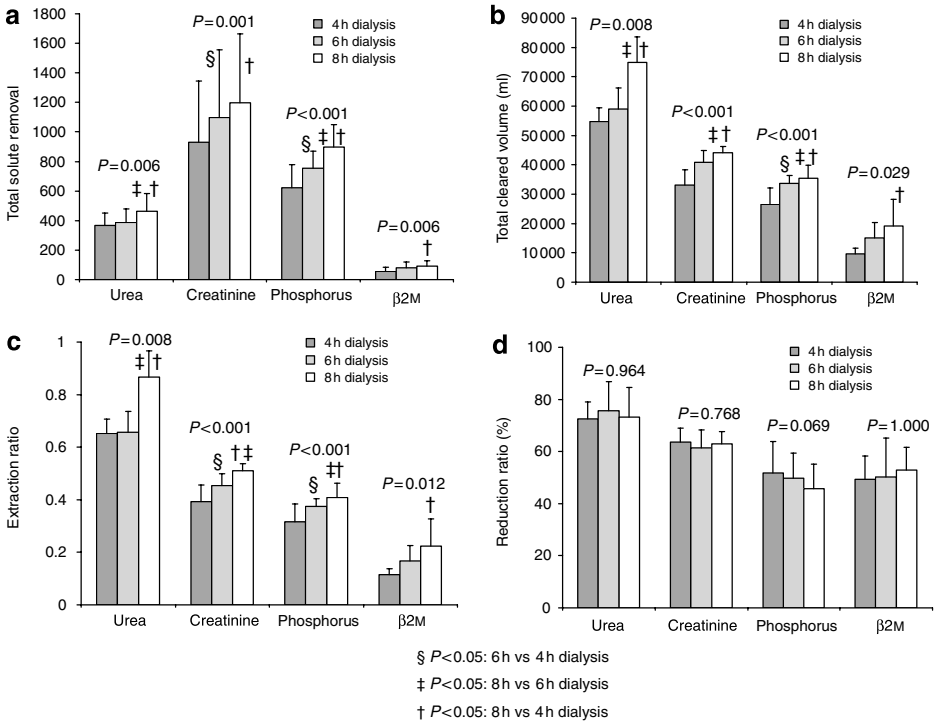

Figure 2 | Removal parameters. (**a**) Total solute removal (mg, except for urea in 0.1 g), (**b**) total cleared volume (ml), (**c**) dialyzer extraction ratio, (**d**) and reduction ratio (%) of urea, creatinine, phosphorus, and β2-microglobulin for the 4, 6, and 8 h dialysis session.

reduction ratio for all solutes under study. Furthermore, Kt/V_{urea} values were 1.39 ± 0.28, 1.60 ± 0.59, and 1.51 ± 0.49 for the 4, 6, and 8 h dialysis (not significant). Figure 3 illustrates the reduction ratio at different time points during the 4, 6, and 8 h dialysis sessions for urea, creatinine, phosphorus, and β2-microglobulin. The reduction ratio is progressively increasing for urea, creatinine, and β2-microglobulin, and a difference in post-dialysis reduction ratio compared to the value at 120 min was found during the 4, 6, and 8 h dialysis, respectively, for urea (all $P = 0.008$), CTN (creatinine) (all $P = 0.008$), and during the 4 h dialysis for β2-microglobulin ($P = 0.031$). For phosphorus (all sessions) and β2-microglobulin (6 and 8 h dialysis), however, RR remains constant from the 120th minute on for all sessions, and in individual patients, even an intradialytic rebound of phosphorus was observed.

The percentage increase of TSR, TCV, dialyzer extraction ratio, and reduction ratio during a dialysis session of 6 and 8 h compared to 4 h dialysis is given in Table 1. Significant differences were found between the percentage increases during 8 h dialysis compared to the increases during 6 h dialysis for TSR of urea ($P = 0.012$) and phosphorus ($P = 0.039$), for TCV of urea ($P = 0.016$), creatinine ($P = 0.008$), and phosphorus ($P = 0.012$), and for the dialyzer extraction ratio of urea ($P = 0.016$), creatinine ($P = 0.008$), and phosphorus ($P = 0.012$). No differences were found for the reduction ratio, although it should be considered that standard deviations on the percentages were substantial, resulting in a low power at statistical testing.

Finally, as the urea dialyzer clearances at the end of dialysis were not significantly different from those at 5 min, and variations were even inconsistent, efficient Genius operation without recirculation of spent dialysate was obtained for all applied dialysis time schedules over the entire observation period.

DISCUSSION

Although most studies evaluate the impact of dialysis time on solute removal by varying more than one parameter affecting dialysis adequacy, we investigated the isolated effect of time on the removal of urea, creatinine, phosphorus, and β2-microglobulin, and this using different modalities to express dialysis adequacy. Patients were undergoing three different dialysis sessions with the Genius system, lasting for 4, 6, and 8 h, respectively, whereas total volume of processed blood and dialysate remained the same.

The most striking result of this study is that protracting dialysis time results in a higher total amount of solute removed from the patient's body, whereas Kt/V_{urea} is not able to detect this difference.

Although previous studies illustrated the positive impact of longer dialysis only for the removal of solutes such as β2-microglobulin[4–6] and phosphorus,[3,7,9,11,12] we found that prolonged dialysis is also effective for small and water-soluble solutes such as urea and creatinine. This result is remarkable, as we were dealing with an equal amount of processed blood in all sessions. The significant larger TSR and TCV for longer dialysis, however, conform with the fact that the dialyzer extraction ratio, which is a relative clearance, also was higher. This can be attributed to a higher driving force for mass transfer in the dialyzer, as dialyzer inlet concentrations remain higher for slower and longer dialysis due to more

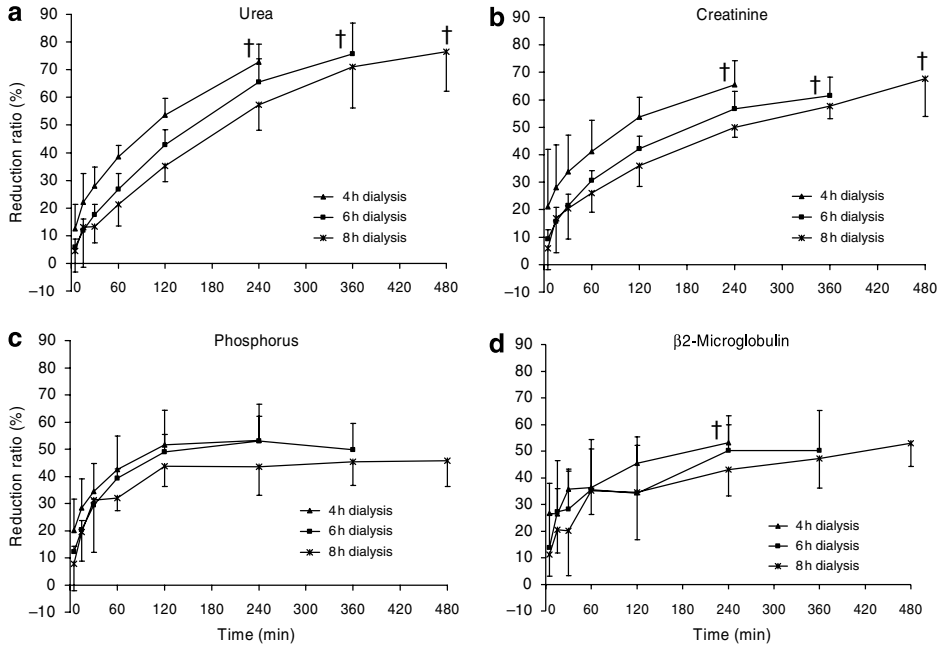

Figure 3 | Reduction ratio. Reduction ratios at different time points during the 4, 6, and 8 h dialysis sessions for (**a**) urea, (**b**) creatinine, (**c**) phosphorus, and (**d**) β2-microglobulin.

Table 1 | Percentage increase of TSR, TCV, dialyzer ER, and RR during a dialysis session of 6 and 8 h compared to 4 h dialysis

	TSR		TCV		ER		RR	
	6 vs 4 h	8 vs 4 h	6 vs 4 h	8 vs 4 h	6 vs 4 h	8 vs 4 h	6 vs 4 h	8 vs 4 h
Urea	6.1	26.1†	0.7	33.3†	1.0	33.2†	4.1	1.1
CTN	21.7	35.5	16.7	32.1†	17.1	32.0†	−2.9	−0.3
P	26.7	48.9†	22.4	32.5†	22.7	32.4†	2.1	−5.8
β2M	42.5	81.2	48.5	94.4	48.9	94.3	5.2	9.3

β2M, β2-microglobulin; CTN, creatinine; ER, extraction ratio; RR, reduction ratio; P, phosphorus; TSR, total solute removal; TCV, total cleared volume.
†$P<0.05$ percentages '8 vs 4 h' vs '6 vs 4 h.'

pronounced concentration shifts during dialysis from the tissue toward the blood and plasma compartment. Furthermore, as a decreased dialysate flow, as the only changed parameter, results in a smaller extraction ratio,[18,19] whereas a decreased blood flow is known to barely improve extraction from the dialyzer in case of pure diffusive transport, our study clearly indicates that the time factor plays the major role compared to the changes in applied flow rates. However, it should be remarked that total solute removed during two successive 4 h dialysis sessions at high flow rates might be higher than that during a single prolonged dialysis session of 8 h at decreased flow rates.

Although urea reduction ratio and Kt/V_{urea} are often used to estimate dialysis adequacy, this study did not find any differences in these values, in spite of the significantly larger TSR during prolonged dialysis. As slowing down dialysis flows allows more shifts of solute out of the extraplasmatic compartments, compartmental behavior of the different solutes will be different when dialysis duration is extended, allowing a higher absolute amount of solute removal in spite of no differences in RR and Kt/V_{urea}. Quantifying the adequacy of different dialysis strategies only with the use of Kt/V_{urea} or urea reduction ratios will thus lead to erroneous conclusions, if the time frame of the tested modalities is different. This finding is not surprising for phosphorus, as the removal of phosphorus has previously been described by a four-compartmental kinetic model,[20] where the third and fourth compartment release phosphorus in the extracellular and intracellular compartment, respectively, after the intracellular concentration drops below a threshold concentration. This phenomenon is reflected by the stabilization of phosphorus concentration during the course of dialysis (Figure 3). However, the impact of long and slow dialysis on solutes such as urea, creatinine, and β2-microglobulin, which are rather following a two-pool model,[4,21–25] was also significant.

This finding conforms to the results of a theoretical study based on kinetic modeling of different small and water-soluble compounds.[2,26] It was revealed that solutes that are distributed in a small total volume and behave like one-compartmental solutes take most advantage of short daily dialysis sessions, whereas solutes characterized by a large total distribution volume divided into at least two compartments take more advantage of a prolonged dialysis treatment, three times a week. The major clinical impact of such a prolonged dialysis is the attenuated post-dialysis rebound phenomenon and the lower mean solute concentration in the patient. Thus, overall uremic toxicity is lower resulting in less adverse uremic effects and improved patient well-being. Furthermore, accounting for the present results as well as for the native kidney function, it is obvious that the lowest mean patient concentrations are registered for a daily prolonged dialysis.

Hence, our data underscore the importance of improving dialytic removal by modifying relevant parameters inducing beneficial kinetic shifts and enhancing removal out of second or even more distal compartments.

Finally, it should be remarked that the presented data is based on the results of a single dialysis session of each investigated time schedule with a limited number of patients. Nevertheless, our study clearly indicates that a prolonged dialysis session is favorable compared to standard 4 h dialysis, due to the larger amount of solute removal and a decreased solute content in the patient in the interdialytic period.

Conclusion

Although several studies have already reported about the importance of time in the removal of difficult-to-remove uremic retention solutes, the factor time was not the only parameter with a potential impact on adequacy that was modified in those studies. Therefore, we investigated the isolated effect of the time factor on the removal and kinetic behavior of different molecules such as urea, creatinine, phosphorus, and β2-microglobulin. For the different sessions lasting 4, 6, and 8 h, reduction ratios were not significantly different, whereas TSRs, dialyzer extraction ratios, and TCVs were higher for prolonged dialysis.

Hence, while applying Kt/V_{urea} or reduction ratio as parameters to indicate dialysis adequacy, important errors can be made when comparing dialysis sessions of different time durations.

MATERIALS AND METHODS

Patients and dialysis strategies

Nine stable chronic hemodialysis patients (five women and four men) with a mean age of 71 ± 10 years and a mean weight of 79 ± 12 kg were studied. The study was approved by the local ethics committee and written informed consent was obtained.

Before the experiments, patients were regularly dialyzed during 19 ± 12 months on Genius hemodialysis ($n=6$) or standard hemodialysis ($n=3$) for a mean duration of 243 ± 10 min per

Table 2 | Characteristics of the FX80 high-flux dialyzer

Inner lumen	μm	185
Wall thickness	μm	35
Surface area	m^2	1.8
Ultrafiltration coefficient	ml per h per mm Hg	59
Sieving coefficient (–) (Q_B 300 ml min^{-1}; Q_{UF} 60 ml min^{-1})		
Inulin		1
β2-Microglobulin		0.8
Albumin		0.001
Clearances (ml min^{-1}) (Q_B 300 ml min^{-1})		
Urea		276
Creatinine		250
Phosphorus		239
Vitamin B12		175
Inulin		125

Q_B, function of blood flow rate; Q_{UF}, function of ultrafiltration.

session with an FX80 ($n=5$), FX60 ($n=1$), or F8HPS ($n=3$) dialyzer. In this pre-experimental phase, blood flows were set at 350 ml min^{-1}; dialysate flow was 350 ml min^{-1} in the case of Genius dialysis and 500 ml min^{-1} with standard dialysis.

In this study, each patient was dialyzed on three different occasions using the Genius single pass batch system (Fresenius Medical Care, Bad Homburg, Germany) with high-flux Fresenius FX80 dialyzers. The characteristics of the dialyzer are detailed in Table 2. Dialysis sessions were each time performed on the same day of the week, whereas a washout period of 2 weeks was applied in between the experimental dialysis sessions. Each patient served as his/her own control and no alterations in diet or dosing of phosphate binders and vitamin D analogues were allowed during the test period.

The experimental sessions lasted 4, 6, or 8 h and were assigned in random order. Blood flows were set at 350, 250, and 180 ml min^{-1} with the 4, 6, and 8 h dialysis session, respectively, to obtain a similar amount of waste dialysate volume. Ultrafiltration rates were set to the needs of the patients and were equal to 0.36 ± 0.19 l h^{-1} (4 h session), 0.24 ± 0.16 l h^{-1} (6 h session), and 0.21 ± 0.11 l h^{-1} (8 h session). The composition of the dialysate was 35 mmol l^{-1} bicarbonate, 140 mmol l^{-1} sodium, 111.5 mmol l^{-1} chloride, 5.5 mmol l^{-1} glucose, 0.084 mmol l^{-1} citrate, 1.25 mmol l^{-1} calcium, 0.5 mmol l^{-1} magnesium, 2.252 mmol l^{-1} hydrogen; potassium concentration was adapted following the needs of the patient. Total volume of waste dialysate, including the ultrafiltrate volume, was read from the Genius monitor.

Blood and dialysate sampling

For each patient, blood samples were taken from the inlet blood lines immediately before the onset of dialysis, and at 5, 15, 30, 60, 120, 240 min during the 4, 6, and 8 h sessions. An additional sample was taken at 360 min during the 6 and 8 h session and at 480 min during the 8 h session. Blood samples were immediately centrifuged during 10 min at 1900 *g* (CR 412; Jouan, Saint-Herblain, France), after which the plasma was stored at −80 °C until analysis for urea, creatinine, phosphorus, and β2-microglobulin. From the outlet dialysate line, dialysate was sampled at 5, 15, 30, 60, 120, 240 min (4, 6, and 8 h session), 360 min (6 and 8 h session), and at 480 min (8 h session). Furthermore, at the end of dialysis, a sample was taken from the ultrafiltrate recipient (Figure 1—point 3) after thorough mixing to quantify solute concentration in total spent dialysate.

Analyses

Urea concentrations were determined by a kinetic UV assay for urea/urea nitrogen (Roche Diagnostics GmbH, Mannheim, Germany) and were measured photometrically at 340 nm (Genesys 10vis; Spectronic Unicam, Rochester, NY, USA). Creatinine was analyzed by the Jaffé reaction using Roche reagents that are Isotope Dilution Measurement Standardized (IDMS) and measured photometrically at 540 nm with the Creatinine Analyzer 2 (Beckman Instruments, Fullerton, CA, USA). Phosphorus concentrations were determined with a Modular analyzer (Roche Diagnostics GmbH) and measured photometrically at 340 nm. Quantitative determination of β2-microglobulin in serum and dialysate samples was performed using an Elisa kit (Orgentec Diagnostika, Mainz, Germany) according to the manufacturer's guidelines, except for an additional 1:3 dilution of the samples, because of the higher concentrations due to renal failure. Photometrical reading was performed at 450 nm with a reference at 630 nm (EL 808; Bio-Tek Instruments, Winooski, VT, USA).

Calculation of total solute removal

From the total spent dialysate concentration at the end of dialysis ($C_{D,end}$) and accounting for the total waste dialysate volume ($V_{D,end}$), total solute removal (TSR) (mg) was calculated as

$$TSR = C_{D,end} V_{D,end} \quad (1)$$

Per patient, the obtained TSR values for the 6 and 8 h session were normalized for the total waste dialysate volume, $V_{D,end}$, as recorded during the 4 h dialysis. This procedure was needed to account for small differences in $V_{D,end}$ during 4 h dialysis compared with the 6 and 8 h sessions.

Calculation of clearance in the dialyzer

From the mass balance in a dialyzer, clearance K (ml min^{-1}) can be written as a function of blood flow rate Q_B (ml min^{-1}) and geometrical dialyzer characteristics:[27]

$$K = \frac{1 - \exp(-\beta L_F)}{1 - \alpha \exp(-\beta L_F)} Q_B \quad (2)$$

with L_F (m) the fiber length, α (dimensionless) the ratio of blood and dialysate flow rate, and parameter β (1/m) defined as a function of overall mass transfer coefficient K_0 (m s^{-1}), and the summation of the perimeters of all fibers P_F (m):

$$\beta = \frac{K_0 P_F}{Q_B}(1 - \alpha) \quad (3)$$

in which the overall mass transfer coefficient K_0 is derived from the mass balance in between the dialysate outlet concentration, C_{Do}, and the blood inlet concentration, C_{Bi}, accounting for a parameter α approaching unity:[27]

$$K_0 = \frac{C_{Do}}{\alpha L_F P_F (C_{Bi} - C_{Do})} Q_B \quad (4)$$

Calculation of total cleared volume

Total cleared volume (TCV) (ml) was calculated as a function of dialyzer clearance K (ml min^{-1}) and dialysis duration t (min):

$$TCV = Kt \quad (5)$$

To compare results for the same amount of processed blood, the results for the 6 and 8 h sessions were normalized for the processed blood volume as recorded during the 4 h dialysis.

Calculation of dialyzer extraction ratio

To obtain an idea about the removal capacity of the dialyzer irrespective of blood flow rate Q_B, we considered the dialyzer extraction ratio (ER) (dimensionless) as well, defined as dialyzer clearance K normalized by blood flow Q_B:[28]

$$\mathrm{ER} = \frac{K}{Q_B} \tag{6}$$

Calculation of reduction ratio

In analogy with the definition for the urea reduction ratio, URR, reduction ratio (RR) (%) of creatinine, phosphorus, and β2-microglobulin were defined as a function of pre-dialysis concentration (C_{pre}) and concentration at different time points during dialysis (C_{tx}) of samples taken at the dialyzer inlet:

$$\mathrm{RR} = \frac{C_{pre} - C_{tx}}{C_{pre}} 100 \tag{7}$$

Calculation of Kt/V_{urea}

Single pool Kt/V_{urea} was computed using the Daugirdas equation:[29]

$$\mathrm{sp}\frac{Kt}{V_{urea}} = -\ln\left[\frac{C_{post}}{C_{pre}} - 0.008t\right] + \left[\left(4 - 3.5\frac{C_{post}}{C_{pre}}\right)\left(\frac{\mathrm{UF}}{\mathrm{BW}_{post}}\right)\right] \tag{8}$$

with C_{post} and C_{pre} post- and pre-dialysis urea concentrations, t dialysis duration (h), UF (ultrafiltration) volume (kg), and BW_{post} post-dialysis body weight of the patient (kg).

Calculation of percentage increase

The percentage increase of TSR, TCV, dialyzer extraction ratio, and reduction ratio during a dialysis session of 6 and 8 h dialysis compared to 4 h dialysis was calculated.

Statistical analysis

Data were analyzed using SigmaStat software (Jandel Scientific, San Rafael, CA, USA). Data are expressed as mean ± s.d. Statistical analyses were carried out using the non-parametric Wilcoxon signed rank test for paired samples and Friedman repeated measures analysis of variance on ranks. A P-value of <0.05 was taken the limit of significant difference.

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