

Effect of Blood Supply to the Filter on the Clearance of Small Molecular Weight Toxins during Conventional Hemodialysis

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Abstract

Introduction: The aim of this study was to investigate the benefit of using a high blood supply to the filter in terms of clearance of small molecular weight toxins during conventional hemodialysis. **Patients-Methods:** We studied 23 hemodialyzed patients (12M, 11F) over 18 years of age, (aged from 44 to 93 years, mean \pm SD = 65.1 \pm 12.6), on conventional hemodialysis (for 15 to 455 months, mean \pm SD = 88 \pm 113), used a blood supply of 300 or 400 ml/min to the filter, with surface area of 2.1 m², determining Kt/V and URR, as well as the potassium, urea, creatinine and b₂-microglobulin removal, in two dialysis sessions separated by one week (with collection of the hole ultrafiltrate in each of the two dialysis sessions). The same filter was used in both cases and the same dialysate, in 4-hour sessions in all cases. **Results:** A statistically significantly better removal of small molecular weight toxins (Kt/V and URR) was found with the 400 ml/min blood pump ($p < 0.001$, in both cases), as well as and for urea removed ($p < 0.005$), and a numerically higher b₂-microglobulin removal in the same blood supply. **Conclusion:** It appears that higher blood supply contributes to better removal of low molecular weight toxins and numerically also of b₂-microglobulin. The potassium removed seems to be relatively small compared to the usual daily intake, when the potassium of the dialysate is 3 mmol/L, which probably means its significant removal achieved by large intestine.

Keywords

Low Molecular Weight Toxins, Kt/V, URR, b₂-Microglobulin, Conventional Hemodialysis

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1. Introduction

In daily practice regarding hemodialysis, there is a long delay in implementing changes in conditions which are valid and applicable throughout the world. These improvements, despite being documented, are very slow to implement in clinical practice and this is mainly due to nephrologists and fewer to hemodialyzed patients. Usually, they use filters with small surface area, despite larger ones that provide better toxins clearances have no negative reason to use them. Nephrologists use low blood pumps (providing subtherapeutic levels of toxin clearances), while studies have shown that there is no contraindication for the use of high blood supply to the filter, while at the same time there is a proven clinical benefit.

Thus, many studies have shown that a $Kt/V \geq 1.2$ and a $URR \geq 65\%$ are effective in improving the prognosis of hemodialyzed patients [1] [2]. And because the urea distribution space (V) is constant for the patient, Kt/V can only be increased by increasing urea clearance (K), duration of session (t) or increase both of them. On the other hand, it is known that the clearance of a low molecular weight (MW) toxin depends on the blood supply to the filter. In this study, we wanted to investigate how the clearance of low MW toxins is affected by changing the blood supply to the filter. In all patients, we used a blood flow rate of 300 or 400 ml/min, with a constant flow rate of the dialysate (500 ml/min) of the same composition, with the same filter and the same duration of session (4 hours), determining the removed toxins and molecules in the total ultrafiltrate, which we collected in a special volumetric barrel.

2. Patients Methods

2.1. Patients

The study included hemodialyzed patients (12M, 11F) over 18 years old, who were on a three-weekly 4-hour/session program, who had been on dialysis for at least one year, who were hemodynamically stable (tolerating the dialysis session well, without having intradialytic hypotensive episodes) and who did not have any known cardiovascular disease.

From the study were excluded pregnant women, patients with significant residual renal function ($GFR > 2.0$ ml/min), hemodynamically unstable with a symptomatic decrease of systolic blood pressure below 100 mmHg or a symptomatic decrease of systolic blood pressure ≥ 30 mmHg, as well as those who did not had the possibility to achieve the goal of high blood supply without problems. The study was approved by the Scientific Council of Komotini General Hospital (Number 4/2024) and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Humans. Written informed consent was obtained from each patient for participation, after they had been informed about the study protocol.

2.2. Methods

All patients were on a conventional hemodialysis program. The filters used were

polyethersulfone (Polynephron low-flux, Elisio-M series, with $K_{uf} = 27$ ml/h/mmHg and $K_{oA} = 1239$ ml/min), with a surface area of 2.1 m². Two dialysis sessions were performed on each patient on midweek days (Wednesday or Thursday), which were separated by one week. The blood pump on the first occasion was 300 ml/min and on the second 400 ml/min, while the dialysate flow was constant at 500 ml/min in all cases. The dialysate used was of the same composition for each patient in both sessions (potassium 3 mmol/L, sodium 140 mmol/L, chlorine 110 mmol/L, calcium 1.5 mmol/L, bicarbonate 33 mmol/L, magnesium 0.75 mmol/L, glucose 5.5 mmol/L and acetate 3 mmol/L).

Low molecular weight heparin (vemiparin) was used as an anticoagulant at a dose of 2500 and 3500 IU depending on the body weight of the patients. The duration of the dialysis session both times was consistently the same for each patient (4 hours). The machines used were Nikkiso DBB EXA.

Blood samples were taken for determination of urea, creatinine, total proteins, albumin, potassium, calcium, prolactin and b₂-microglobulin, both before (from the arterial fistula at the start of the dialysis session) and after one hour from the end of the session from a peripheral vein (to achieving urea equilibration between the extracellular and intracellular space).

The total ultrafiltrate was collected at each dialysis session and from each patient in a suitable volumetric stainless barrel. After the end of each session and after stirring the ultrafiltrate for 10 minutes with an electric stirrer, a sample was taken for urea, creatinine, potassium and b₂-microglobulin.

An Abbott Alinity C analyzer was used to measure the parameters studied. Beta₂-microglobulin determined photometrically. The Daugirdas II formula [3] and the urea reduction ratio (URR) were used to evaluate the effectiveness of hemodialysis. The URR was calculated with the following equation:

$$URR = \frac{\text{Substance}_{\text{Pre}} - \text{Substance}_{\text{Post}}}{\text{Substance}_{\text{Pre}}} \times 100$$
 (where the substance was urea).

2.3. Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation (mean \pm SD) or median (range), according to normality of the distribution of each variable. Comparisons between the groups were performed using the paired t-test (two tailed) and Wilcoxon signed-rank tests if data were non-normal. The analysis was conducted with the Statistical software MedCalc (version. 20.218). Probability values of $p < 0.05$ were considered statistically significant for all comparisons.

3. Results

A total of 23 patients were included in the study. The primary renal disease was glomerulonephritis (5), diabetic nephropathy (6), polycystic kidney disease (2), hypertensive nephrosclerosis (2), lupus nephropathy (1), lithium nephropathy (1), single kidney (1), nephrolithiasis (1), and unknown cause (4). Only two had residual diuresis, with $GFR < 2$ ml/min. The patients' age, body weight, body wa-

ter, body surface area, and duration on dialysis are shown in **Table 1**.

Table 1. It appears the ages, body weights, body water and body surface area of each patient, as well as the duration of renal replacement therapy of them.

P/s	Age (y/s)	Body weight (kg)	Body water (L)	Surface area (m ²)	Duration of dialysis (months)
1	48	74.0	42.5	1.95	76
2	69	67.5	37.2	1.80	263
3	44	95.0	30.5	2.03	26
4	68	59.5	34.6	1.70	455
5	70	59.5	36.7	1.70	66
6	85	84.0	40.7	1.91	24
7	83	54.0	27.5	1.49	31
8	51	70.0	33.1	1.79	56
9	53	72.0	31.7	1.67	48
10	62	78.0	41.0	1.90	124
11	71	77.5	33.8	1.95	150
12	65	71.5	38.5	1.82	92
13	44	95.5	39.0	2.02	27
14	64	88.0	41.6	1.95	36
15	60	81.0	30.0	1.88	34
16	82	65.0	34.5	1.68	22
17	60	69.0	38.2	1.80	16
18	60	52.0	27.4	1.65	359
19	93	74.5	32.5	1.71	15
20	62	96.0	44.3	1.98	16
21	78	77.0	33.5	1.76	21
22	63	87.0	36.3	1.88	27
23	62	54.0	17.9	1.61	42
Mean \pm SD n = 23	65.1 \pm 12.6	74 \pm 12.8	34.9 \pm 5.8	1.81 \pm 0.14	88 \pm 113 (from 15 to 455)

A significantly higher Kt/V (1.63 ± 0.21 Vs 1.48 ± 0.19 , $p < 0.001$), or 12.8% increment and URR (74.5 ± 5.6 Vs 71.6 ± 5 , $p < 0.001$), were found in the group with the increased blood flow (group 400 ml/min) compared to the blood flow of 300 ml/min, while no significant difference was found in the amount of b₂-microglobulin removed (despite, it was arithmetically greater in the group with blood flow of 400 ml/min pump) and potassium (**Table 2**).

Table 2. It appears the levels of Kt/V, URR, the amount of b₂-microglobuline (mg/L), potassium (mmol/L), urea (mg) and creatinine (mg) removed in each patient in the ultrafiltrate during hemodialysis sessions with a 300 or 400 ml/min pump.

P/ts	Kt/V		URR (%)		Serum b ₂ -microglobuline removed (mg)		Potassium removed (mmol)		Removed amount of urea (mg)		Removed amount of creatinine (mg)	
	Group 300	Group 400	Group 300	Group 400	Group 300	Group 400	Group 300	Group 400	Group 300	Group 400	Group 300	Group 400
1	1.20	1.25	64.1	66.2	25.8	30.4	44	41	28,638	32,927	2412	2102
2	1.35	1.58	68.8	75.2	25.8	126	43	65	19,479	21,118	1767	1722
3	1.29	1.52	66.3	63.3	34.0	24.6	75	58	25,422	30,010	1251	1205
4	1.52	1.66	73.6	76.5	25.2	85.9	56	67	30,870	49,580	1348	1448
5	1.60	1.48	73.7	71.4	25.5	24.7	73	35	25,996	31,220	1353	1468
6	1.26	1.58	67.4	75.2	38.1	30.4	46	41	19,926	39,935	1058	1507
7	1.51	1.76	73.7	78.9	22.1	31.2	141	59	22,263	23,798	812	1084
8	1.65	1.67	75.7	75.9	23.2	16.1	42	86	29,890	35,340	1550	2046
9	1.60	1.85	75.6	80.0	24.6	24.6	53	46	20,135	23,493	1009	1132
10	1.18	1.37	63.7	69.8	25.8	25.8	92	92	26,040	25,026	1314	1484
11	1.29	1.47	66.3	71.6	28.0	27.4	163	73	20,700	22,605	1652	1315
12	1.39	1.43	69.1	72.7	31.2	24.8	68.4	74.0	27,846	24,180	1676	1513
13	1.29	1.52	66.3	63.3	34.0	24.6	53.0	58.0	25,432	30,012	1251	1193
14	1.12	1.55	62.0	72.4	25.9	18.5	80	70.5	25,900	27,060	1140	1292
15	1.57	1.74	74.5	77.7	12.4	18.6	36.8	61.6	34,100	28,396	980	1079
16	1.54	1.6	73.7	74.8	24.6	31.2	33.6	40.0	24,108	27,412	1476	1595
17	1.47	1.52	72.9	74.1	24.6	24.3	46.0	16.7	27,429	33,048	1316	1458
18	1.71	1.65	76.8	77.6	30.5	24.6	30.0	21.0	22,570	24,840	720	689
19	1.69	2.18	77.1	85.0	18.5	30.9	46	22.5	27,921	26,284	836	1024
20	1.55	1.44	73.9	71.4	24.6	18.3	21.3	42.6	25,092	25,986	800	854
21	1.74	2.0	77.8	82.2	24.6	31.0	33.6	24.4	947	8680	726	719
22	1.69	1.95	76.9	81.8	30.4	24.6	28.8	33.6	9841	16,482	693	1021
23	1.75	1.67	77.8	76.4	24.3	31	17.6	24.4	13,729	17,112	948	843
Mean ± SD n = 23	1.48 ± 0.19	1.63 ± 0.21	71.6 ± 5	74.5 ± 5.6	26.2 ± 5.3	32.6 ± 24.3	57.5 ± 35.4	50.1 ± 21.6	23,229 ± 7089	27,154 ± 8060	1221 ± 407	1295 ± 366
	<i>p</i> = 0.001 (increase 12.8%)		<i>p</i> = 0.001 (increase 4.1%)		<i>p</i> = NS		<i>p</i> = NS		<0.005		<i>p</i> = NS	

What is of particular interest is the amount of potassium removing through the filter in each of the dialysis session (with a 300 or 400 ml/min pump). In the case of blood supply of 300 ml/min, removal from 17.6 mmol to 141 mmol was found,

and with a supply of 400 ml/min, removal ranged from 16.7 mmol to 86 mmol *i.e.* was arithmetically higher with the low blood flow (57.5 ± 35.4 Vs 50.1 ± 21.6 , $p = \text{NS}$).

The amount of urea removed with a 300 ml/min pump was $23,229 \pm 7089$ and with pump 400 was $27,154 \pm 8060$ ml/min ($p < 0.005$), while the amount of creatinine removed with a 300 ml/min pump was 1221 ± 407 and with 400 ml/min was 1295 ± 366 ($p = \text{NS}$) (**Table 2**).

4. Discussion

Factors that can increase Kt/V and URR are increasing the filter surface area, increasing blood supply or dialysate supply to the filter, and increasing the duration of the session (the latter being more difficult for dialyzed patients to accept). It is noted that the NKF-K/DOQI guidelines consider a blood flow of less than 300 ml/min to provide inadequate clearance [4] [5].

In 21 hemodialyzed patients, increasing the blood supply to the filter by 30% (from 200 ml/min to 300 or 400 ml/min), using dialyzers of the same composition and surface area with the same dialysate flow, resulting in a 23% increase in URR, as well as Kt/V [6]. In Japan, Yamamoto *et al.* studied 22 hemodialyzed patients for 2 years. In the first year, they applied a blood flow of 200 ml/min and in the second year, 400 ml/min with the same dialysate flows and the same dialyzers in both periods. The increased blood flow increased Kt/V and contributed significantly to the reduction of urea nitrogen ($p = 0.015$), something similar that we also noticed in this study and serum creatinine levels ($p = 0.005$) [7].

Other researchers have also noted similar results with lower maximum blood flows. Thus, Kim *et al.*, increasing the blood flow in 36 patients from 230 ml/min by 15% in those with a body weight < 65 kg and by 20% in those with a weight > 65 kg, and found a significant increase in the mean levels of Kt/V (from 1.02 ± 0.09 to 1.14 ± 0.12 , $p < 0.001$), as well as in the mean value of URR (from 56.9 ± 4.0 to $60.8 \pm 4.1\%$, $p < 0.001$) [8]. Others studied the attributable clearance with blood flows of 200 and 250 ml/min in 42 hemodialyzed patients. They found that with a blood flow of 200 ml/min, 16.7% had a Kt/V higher than 1.3 and a URR higher than 65%, while with a blood flow of 250 ml/min, 26.2% of patients had a Kt/V higher than 1.3 and 35.7% had a URR higher than 65%, a significant difference in both cases [9], *i.e.* they found an improvement in the clearance of small molecular weight toxins. Chang *et al.* in a prospective, multicenter study with 1129 hemodialyzed patients, during the last 30 months, studied a group with 271 patients who were being dialyzed with a blood flow < 250 ml/min (mean \pm SD = 218 ± 17) and another of 858 patients with a blood flow \geq 250 ml/min (mean \pm SD = 272 ± 24). They found a statistically significantly higher Kt/V in the group with the increased blood flow (1.44 ± 0.29 Vs 1.49 ± 0.30 , $p = 0.017$) [10]. Also, Rafik *et al.* studied 22 hemodialyzed patients with blood flow of 250 and 350 ml/min. They found a higher Kt/V in the patients with the highest flow ($p < 0.05$) [11]. Accordingly, Abdulla *et al.* who studied hemodialyzed patients, using blood flows

of 200 ml/min, 250 ml/min and 300 ml/min, found the highest Kt/V and URR at a blood flow of 300 ml/min [12]. Furthermore, Afzal *et al.* studied a total of 40 hemodialyzed patients with two different blood flows (300 and 350 ml/min) during corresponding sessions for a period of one month. Blood samples were taken shortly before the start of each dialysis session and 45 min after the end, to determine urea levels. Increasing the blood flow from 300 to 350 ml/min resulted in an increase in URR from 53% to 60% ($p < 0.05$) [13], levels which were apparently again subtherapeutic. Another study in 166 hemodialyzed patients found that increasing blood flow had a significant impact on Kt/V and therefore on the adequacy of hemodialysis. The mean Kt/V of the 250 ml/min group was 1.35 ± 0.37 , the 300 ml/min group was 1.59 ± 0.36 , and the 350 ml/min group was 1.70 ± 0.37 (the differences between groups were statistically significant). According to these findings, increasing both blood and dialysate flow (from 500 ml/min to 800 ml/min) resulted in a significant increase in Kt/V and dialysis efficiency [14].

Finally, the studies mentioned confirm that the increase in blood flow is associated with an increase of clearance of low molecular weight toxins, however, most of them refer to pumps up to 350 ml/min (except for one that reached 400 ml/min) (6) and another one, which concerned Japanese patients, who are known to have a relatively smaller body mass index than European or American patients (7). In our study, the same patients were assessed with pumps of 300 or 400 ml/min, in dialysis sessions of the same duration, with the same filter (and surface area) and the same dialysate flow, and a significant increase in Kt/V ($p = 0.001$) and URR ($p = 0.001$) was found, determining urea one hour after the end of the session. And it is of course important that from the determination of removed amount of urea this was statistically significantly higher with the high blood pump ($p < 0.005$). Importantly, a positive impact on survival was found with increasing filter blood flow. A study from Korea, with 1129 hemodialyzed patients, showed that blood flow < 250 ml/min was associated with higher mortality (10). In another study also from Korea with 2615 hemodialyzed patients, it was found that higher Kt/V (>1.4) and URR ($>70\%$) were associated with lower all-cause mortality [15].

Regarding the benefit resulting from the increased blood supply to the filter, in addition to the achieved clearance, other parameters also increase. Thus, it was found that this increase of blood supply also has an impact on the amount of b_2 -microglobulin removed. In particular, Leclerc *et al.* who studied 17 hemodialyzed patients, with various blood supply to the filter (300, 400, 450 ml/min), found a higher decrease in b_2 -microglobulin by 5% for each increase in blood supply by 100 ml/min (the decrease of b_2 -microglobulin from 0.40 ± 0.07 reached to 0.45 ± 0.06 and 0.48 ± 0.06 , respectively), a change that was statistically significant ($p < 0.05$) [16], results that others agree with [7], something that we did not find, although there was a numerically greater removal with the blood supply of 400 ml/min (32.6 ± 24.3 Vs 26.2 ± 5.3 , $p = \text{NS}$), perhaps due to the small number of patients in our study and the comparatively lower blood flows that we had. Of course, it is worth noting that any greater amount of medium molecular weight

toxins that are removed is to the benefit of hemodialyzed patients, even if this is not statistically significant.

Regarding the amount of potassium removed, what we found was quite low (57.5 ± 35.4 and 50.1 ± 231.6 mmol), something like what we found in our previous studies (69.7 ± 27.1 mmol) [17] and 73.4 ± 32.8 mmol [18] with conventional hemodialysis. However, Blumberg *et al.* 25 years ago, in their study with 14 hemodialyzed patients, found a slightly greater potassium removal with conventional hemodialysis (107.1 ± 6.0 mmol), where of course they did not accurately determine the potassium in the ultrafiltrate, and it should be noted that when selected their patients, they included only those who repeatedly had serum potassium > 5.5 mmol/L (which favors the higher potassium removal due to the greater gradient between blood and dialysate), the surface area of their filters was 2.0 m^2 , with the duration of session 4 - 5 hours (blood supply of 300 ml/min), with a dialysate that had 1 mmol/L potassium (very lower than ours), 40 mmol/L bicarbonate (higher than ours) and 5.5 mmol/L glucose [19], while in our study all sessions were 4 hours of duration, with filters of surface area 2.1 m^2 , with a dialysate that had 3 mmol/L potassium, 33 mmol/L bicarbonate and the same glucose. These differences raise some questions about whether it is safe to remove less than 100 mmol of potassium every 2 days in a hemodialyzed patient, when his diet usually contains much more potassium, when also many dialysis units in the world use a potassium solution of 3 mmol/L.

Alfurayh *et al.* studied 10 stabilized normotensive hemodialyzed patients with stable normal heart function using ultrasound. They had a personalized dialysate with a flow rate of 700 ml/min. The blood flow rate was chosen to be 250, 350 or 450 ml/min. The results ultimately showed that increasing the blood flow during the dialysis session up to 450 ml/min had no negative effect on the left ventricular and ejection fraction, nor on heart rate and blood pressure. However, whether the increased blood flow to the filter has a significant long-term impact on the integrity of the left ventricular or whether there is an impact in those with ischemic heart disease was not answered by this study [20], results with which others agree also [21].

Similarly, Hafez *et al.* studied the effect of changing the blood supply to the filter on blood pressure, heart rate, and cardiac output in hemodynamically stable patients during a dialysis session in 40 hemodialyzed patients. They found a significant increase in systolic blood pressure at a blood flow rate of 200 ml/min compared to 300 and 400 ml/min, but there was no significant change in systolic blood pressure at 300 ml/min compared to 400 ml/min, which may help reduce intradialytic hypotension [22].

Although the Japanese DOPPS considers that higher blood supply can reduce mortality, Japanese nephrologists are concerned about the increased cardiovascular burden caused by increased blood flow and thus use lower flows. However, with a blood flow of 400 - 500 ml/min, there were no acute changes in heart function or blood pressure [20] [23]. Furthermore, high-efficiency dialysis with blood

flows > 450 ml/min did not increase mortality [24], nor did it increase cardiac deaths in the HEMO study group [25]. In contrast, another study showed that increased blood supply to the filter is important for optimal dialysis dose, while insufficient dose is associated with increased mortality [26]. Although the mechanisms explaining the increased mortality in hemodialyzed patients are not clarified, insufficient dialysis dose promotes arteriosclerosis, infections and malnutrition, which in turn increase mortality [27].

While these differences in blood supply to the filter are present in practice, especially the low ones should be evaluated with the knowledge that the actual blood supply is significantly less than that indicated on the machine and requested by the doctors. The most common cause of this is low blood pressure in the extracorporeal circuit (pressure before the pump or the so-called negative pressure) [28], which depends on the requested blood flow, the diameter and length of the needle used for vascular access (fistula) and the viscosity of the blood. In fact, it is considered that the blood supply to the filter is reduced by 8 - 15% at a negative pressure of -200 mmHg and more than 30% at a negative pressure of -400 mmHg. More specifically, Ward considers that for blood flow rates of 200 - 400 ml/min, the actual flow rate is given by the equation:

$$Q_{\text{Actual flow rate}} = Q_{\text{Pump flow rate}} - 0.22 \times \text{Negative pressure,}$$

while for a pump of 400 - 650 ml/min by the equation:

$$Q_{\text{Actual flow rate}} = Q_{\text{Pump flow rate}} - 0.31 \times \text{Negative pressure.}$$

Thus, although it has been known for many years that an increase in blood supply to the filter is associated with an increase in the clearance given, there are still no Guidelines regarding the optimal blood flow to the filter, and it is also not clear whether this increase is harmful or not for hemodialyzed patients [29]. However, the fact is that today, in USA, patients with a blood supply to the filter of more than 400 ml/min represent 83.6% of hemodialyzed patients, while in Canada and European countries, patients with a blood flow ≥ 250 ml/min cover approximately 98% of hemodialyzed patients [30]. In contrast, in Japan, patients with a blood flow ≥ 250 ml/min represent 18%, while a blood flow of 200 ml/min is usually prescribed [31]. Of course, all of this is happening while researchers have shown that blood flows of 320 ml/min and 380 ml/min would meet the K/DOQI guidelines for the minimally adequate dialysis dose [32].

5. Conclusion

Our study shows that increasing the blood supply to the filter significantly improves the clearance of small molecular weight toxins and numerically also of b_2 -microglobulin. The potassium removed seems to be relatively small compared to the usual daily intake, when the potassium of the dialysate is 3 mmol/L, which probably means its significant removal through the gastrointestinal tract. The literature shows only positive effects from increasing the blood supply to the filter at least up to 450 ml/min, so it would be good for nephrologists to adopt this in-

crease for the better survival of our patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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