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How Much Is the Removed Amount of Potassium with On-Line Hemodiafiltration Affected by the Filter Surface?

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Abstract: Introduction: The potassium removed by various dialysis methods (pre- and post-dilution on-line hemodiafiltration) is not clear in the literature. The aim of the study was to investigate the amount of potassium eliminated with each session of pre- or post-dilution on-line hemodiafiltration with collection of the total ultrafiltrate in a tank. **Materials and Methods:** We studied in 10 dialyzed patients the removal of potassium by a polyetherosulfone dialysis filter. We sought to investigate whether the amount removed is related to filter surface area and type of dialysis. We examined the removal of potassium by on-line hemodiafiltration and post-dilution with high-flux filters, surface areas 2.5 m^2 (Group A) and 2.1 m^2 (Group B). We repeated the same process with low-flux filters with conventional hemodialysis (Group C), as well as with pre-dilution on-line hemodiafiltration and 2.5 m^2 surface area filters (Group D). **Results:** Significantly higher potassium removal was noted with post-dilution on-line hemodiafiltration versus conventional haemodialysis, which was not affected by filter surface area, and also higher with pre-dilution on-line hemodiafiltration versus all other methods. The amounts of removed potassium even exceeded 300 mmol of potassium/dialysis session in some cases. **Conclusions:** It is concluded that, with on-line hemodiafiltration, much higher amounts of potassium are removed (mainly with pre-dilution) compared to conventional haemodialysis. The amount removed is not affected by the surface of the filter. The lower potassium levels of dialysate play an important role in this elimination.

Keywords: on-line hemodiafiltration; potassium; substitution volume; pre-dilution; post-dilution

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1. Introduction

Potassium is an important ion in the balance of hemodialyzed patients, and it is mainly regulated through extrarenal clearance. It is present in many foods and dietary diversions, especially in our country, and it is very easy, especially in the summer, to bring the patients into life-threatening situations. Another significant parameter to achieve a good potassium balance is that this ion is mainly intracellular, which makes it difficult to remove through the filter. It is known that conventional haemodialysis better removes low molecular weight toxins and molecules (by diffusion) [1], while hemodiafiltration (HDF) removes medium molecular weight molecules (by convention). However, others have found that there is no significant difference in the clearance of urea, creatinine, and phosphorus (small molecular weight molecules) between conventional haemodialysis and pre-dilution on-line HDF with a significant increase (by 10–15%) in post-dilution on-line HDF [2]. The observation that patients under HDF do not have elevated serum potassium levels compared to those under conventional haemodialysis before the beginning of dialysis sessions [3] prompted us to investigate how this is achieved. Due to this observation, we

collected the ultrafiltrate/session and measured the amount of potassium removed during on-line HDF (pre- or post-dilution) compared to conventional haemodialysis.

2. Materials and Methods

2.1. Patients

Ten patients were studied (7M, 3F), aged from 48 to 85 years (mean ± SD = 65.5 ± 11, median age = 68.5 years). Their primary renal diseases were glomerulonephritis (four patients), adult-type polycystic kidney disease (two patients), hypertensive nephrosclerosis (one patient), and unknown aetiology (three patients). Six had an internal arteriovenous anastomosis (fistula), three had a graft, and one had a double-lumen jugular vein dialysis catheter. Only three had residual renal function (24 h urine output > 400 mL the day off dialysis) (Table 1). Two out of the ten had factors affecting serum potassium levels, such as diabetes mellitus; seven were taking a selective beta-blocker (these affect Na^+-K^+-ATPase much less compared to non-selective ones) and three patients were receiving T_4 (Levothyroxine). One patient had three of the above conditions, five patients had two, and three patients had none of these conditions.

Table 1. The sex, age, body weight, residual renal function, duration on haemodialysis and hemodiafiltration, dialysate bicarbonates and serum bicarbonates of each patient before one dialysis session.

P/s	Sex (M/F)	Age (Years)	Body Weight (kg)	Session Duration (h)	Residual Renal Function (mL/24 h)	Months in Haemodialysis	Months in Hemodiafiltration	Dialysate Sodium (mmol/L)	Dialysate Bicarbonate (mmol/L)	Serum Bicarbonate (On-Line HDF Post-Dilution with 2.5 m^2 Filter Surface Area) (mmol/L)
1	M	48	74	4.0	500	71	24	138	33	22.8
2	M	69	67.5	4.25	0	258	19	138	31	22.5
3	F	56	73	4.0	100	54	10	138	33	23.8
4	F	57	65	4.25	250	89	24	140	31	22.1
5	M	68	59.5	4.0	0	450	10	140	33	26.8
6	M	70	70	4.0	150	61	10	138	33	22.5
7	M	85	84	4.0	100	19	9	140	31	22.5
8	M	77	85	4.0	750	10	4	138	33	21.6
9	F	72	69	4.0	500	29	8	140	33	22.2
10	M	53	79	4.75	0	417	4	138	31	21.8
Mean ± SD		65.5 ± 11	72.6 ± 7.76	4.12 ± 0.23	3 ≥ 500	145.8 ± 158.5	12.2 ± 7.08	138 = 6 140 = 4	33 = 6 31 = 4	22.9 ± 1.5

Patients had a stable dry body weight for at least four months (range 59–85 kg) and none had metabolic acidosis before the session (Table 1). There was no evidence of gastrointestinal bleeding. None of the patients had any level of metabolic acidosis or very high blood urea concentrations. All of them followed a fixed diet before and during the study, which contained approximately 60–80 mmol of potassium/24 h. Dietary instructions were given to each patient (along with diet manuals in simplified and understandable language). All patients were informed and gave written consent for their participation in the study. This study was approved by the Scientific Council of General Hospital of Komotini (protocol number 2/2022, date: 1 February 2022) and conducted in accordance with the guidelines for good clinical practice and ethical principles of the Declaration of Helsinki.

Patients with cancer, active infection, known cardiovascular disease, or an unstable hemodynamic status during the session were excluded from the study.

2.2. Methods

In all patients, low molecular weight heparin (bemiparin) was used as an anticoagulant factor in doses of 2500–3500 IU/session, depending on the patients' dry body weight. The blood supply (pump) was 400 mL/min for all patients (with a negative pressure < 200 mmHg) and the dialysate pump was 500 mL/min (all patients were dialyzed with Nikkiso DBB EXA machines). Dialysate bicarbonates were 33 mmol/L in six patients and 31 mmol/L in the remaining four, while dialysate sodium was 138 mmol/L in six and 140 mmol/L in four. Dialysate potassium was 2 mmol/L in three patients and in 3 mmol/L in seven, while glucose was 5.6 mmol/L for all of them (note that all dialysis sessions were conducted with a dialysate of fixed composition for each patient). For seven patients, the duration of the session was 4 h, 4.25 h for two patients, and 4.75 h for one patient (Table 1).

Polyethersulfone-polynephron filters (Elisio^{TM} Nipro 2.1 m^2 and 2.5 m^2 high-flux and 2.1 m^2 low-flux) were used. All patients underwent one post-dilution on-line HDF session with a surface area of 2.5 m^2 high-flux filter (Group A) and a second session with a 2.1 m^2 high-flux filter (Group B), followed by a conventional dialysis session with a low-flux filter with surface area of 2.1 m^2 (Group C) and one pre-dilution on-line HDF session with a high-flux filter with surface area of 2.5 m^2 (Group D). The substitution volume used in post-dilution was 25% of the blood pump (i.e., ≥24 L/session), while in pre-dilution, it was 50% of the blood pump (i.e., ≥48 L/session).

At the midweek session (Wednesday or Thursday), a blood sample was taken at the beginning of the session for serum urea and potassium. One hour after the end of the session (for equilibration of the body's urea), a blood sample was taken to determine the same parameters. Also, before each session (in each group), a blood sample was taken from the arterial line to determine total carbon dioxide (bicarbonates).

The ultrafiltrate was collected in a specially made volumetric barrel, where its volume was determined. After the end of the session and after thoroughly stirring the ultrafiltrate with an electric stirrer for 10 min, a sample was taken to determine the serum urea and potassium.

To determine the potassium of the ultrafiltrate, the equation of Blumberg et al. was modified: $K_{Ultrafiltrate}$ (mmol) = $V_{Ultrafiltrate}$ (mL) × ($K_{Ultrafiltrate\ [mmol)}$ − $K_{Dialysate\ [mmol]}$) [4].

For the laboratory exams of the parameters studied, the Abbott Alinity C analyzer was used. Urea was determined by an enzymatic method, potassium with an ion-selective electrode, and total carbon dioxide photometrically.

2.3. Statistical Analysis

Means and standard deviations of Student's *t*-test values were used for the statistical analysis (MedCalc v. 20.218). Significant differences were considered with a significance level of $p < 0.05$.

3. Results

All patients in each group had predialysis serum bicarbonates ≥ 21.6 mmol/L (indicatively, their values before the first session of group A are reported in Table 1). From the serum potassium levels before the beginning of the session in the four groups (a total of 40 determinations), only eight had values between 5.6 and 6.8 mmol/L. The rest of the values were ≤5.5 mmol/L, which is considered important because the tests were conducted in the summer months and, in our country, the dietary challenges regarding potassium during this period are particularly high. It was also found that, after the end of the session, no one had potassium < 3.2 mmol/L (Table 2).

Table 2. Patients, dialysate potassium, serum potassium (before starting and at the end of dialysis session) in each group and removed potassium in each group in the dialysate (Group A = on-line HDF post-dilution with filter 2.5 m^2, Group B = on-line HDF post-dilution with filter 2.1 m^2, Group C = conventional haemodialysis, Group D = on-line HDF pre-dilution with filter 2.5 m^2).

P/s	Dialysate Potassium (mmol/L)	Serum Potassium (mmol/L)								Dialysate Potassium (mmol)			
		Group A		Group B		Group C		Group D		Group A	Group B	Group C	Group D
		Before	End	Before	End	Before	End	Before	End				
1	3	4.8	4.3	4.9	4.2	5.0	4.5	5.3	4.5	123	108	41	177.6
2	2	4.3	3.5	4.5	4.0	4.2	3.6	5.0	4.5	114.6	128.5	65	336
3	3	4.7	3.7	6.8	4.0	4.5	3.8	5.2	3.8	92.6	104	137	197
4	3	5.1	4.4	5.2	4.3	5.5	4.3	5.6	4.0	136	131	83	56
5	2	4.3	3.3	4.6	3.6	4.5	3.3	5.5	4.0	93.5	137	67	305
6	3	5.8	4.7	5.2	4.2	5.5	3.7	5.7	4.1	63	64	34.9	163.5
7	3	5.1	4.1	5.2	3.9	5.2	4.2	5.6	4.3	116	83	41	211
8	3	4.8	4.5	4.5	4.4	4.7	4.3	4.8	4.3	57.9	107	53	184
9	3	4.8	4.4	5.8	4.0	6.2	4.0	4.8	3.2	78	137	92	139.5
10	2	5.5	4.4	5.6	4.4	5.8	4.1	5.5	4.0	180	177.6	120	255
Mean ± SD	-	4.92 ± 0.47	4.13 ± 0.44	5.23 ± 0.67	4.10 ± 0.23	5.11 ± 0.61	3.98 ± 0.35	5.30 ± 0.31	4.07 ± 0.36	105.5 ± 34.8	117.7 ± 30.2	73.4 ± 32.8	202.5 ± 76.8
		$p < 0.001$		$p < 0.0001$		$p < 0.0001$		$p < 0.00002$		p(A-B) = NS p(A-C) < 0.03 p(A-D) < 0.02 p(B-C) < 0.004 p(B-D) < 0.004 p(C-D) < 0.0002			

The amount of potassium removed with on-line HDF (both post- and pre-dilution) was greater compared to conventional haemodialysis (Table 2), but much greater with pre-dilution compared to any other method used [(p(A-D) < 0.002, p(B-D) < 0.005, p(C-D) < 0.0001)]. The amount removed by pre-dilution on-line HDF was almost more than double the other methods and reached very high levels (up to 255, 305, and 336 mmol in three patients, respectively) (Table 2). The greatest potassium losses were noted in a patient with a dialysate bicarbonates of 31 mmol/L, in another with a dialysate bicarbonates of 33 mmol/L who was not receiving drugs affecting Na^+-K^+-ATPase, and in a third who was receiving a beta-blocker and T_4, who had a dialysate bicarbonates of 31 mmol/L. A common feature of these three patients was a low dialysate potassium of 2 mmol/L.

Another finding in our study was that the urea reduction ratio (URR) did not differ between groups, whichever on-line HDF method was applied, where HDF was significantly better than conventional haemodialysis [Group A = 76.0 ± 2.7%, Group B = 76.3 ± 3.2%, Group C = 73.6 ± 3.3% and Group D = 74.8 ± 3.3%, p(A-C) < 0.05 and p(B-C) < 0.05]. These results are particularly important since 1) It was shown that all three dialysis methods (conventional hemodialysis, hemodiafiltration with pre- and post-dilution) used achieved a very high URR, which in the opinion of many nephrologists does not seem reasonable (mainly for HDF pre-dilution), but also for the very high URR observed in conventional hemodialysis. In our opinion, this is attributed to the increased blood flow rate (in conventional hemodialysis it is of great importance), but also to the large volume of substitution fluid (50% of the 400 mL/min of blood flow mentioned above).

4. Discussion

In a classical Western diet, the daily intake of potassium in normal subjects ranges from 100 to 120 mmol/24 h, where 92% and 8% are removed through urine and feces, respectively, to maintain homeostasis in the body. However, balance is achieved without hyperkalemia being detected, even with 10 times the potassium intake, when renal function

is normal [5]. Of course, in end-stage renal disease under haemodialysis, a potassium diet of only 51–77 mmol/24 h (2–3 g/24 h) is recommended [6].

Conventional haemodialysis, among other things, removes the potassium that accumulates between two dialysis session intervals to prevent the occurrence of severe hyperkalemia before the next session, but also to prevent severe hypokalemia during and after the end of the session [7]. The guidelines do not currently provide recommendations regarding the prescription of dialysate potassium; however, many nephrologists apply the "rule of 7", in which the sum of the patient's serum and dialysate potassium concentrations should be approximately 7 mmol/L [8], although there are limited data to support this rule.

From studies with hemodialyzed patients, it has been found that the potassium removed in one session of conventional haemodialysis is just under 100 mmol [9], or slightly more than this amount [4]. This is much more than that of the extracellular space, which constitutes 1/3 of body fluids and contains approximately 4–5 mmol/L of potassium (i.e., for a man weighing 70 kg with 14 L of extracellular water, extracellular potassium is 14 × 4 = 56 or 14 × 5 = 70 mmol). This is mostly lost in the first 60–90 min of the session [4,9,10], depending on several factors and mainly on the potassium concentration of the dialysate (more with low potassium than with high) [4,9,11,12], as we found in pre-dilution on-line HDF.

Consequently, the exchange mechanisms of potassium between the intra- and extracellular space play a central role in potassium removal during the session. The movement of potassium through the cell membrane takes place through passive diffusion from the intra- to the extra-cellular compartment and in the opposite direction to the action of the Na^+-K^+-ATPase (active transport). The activity of this pump mainly depends on the extracellular concentration of potassium, which changes significantly during the session.

Other metabolic variables that may affect the movement of potassium between intra- and extra-cellular space [13,14] include the rapid correction of acid-base balance (metabolic acidosis) and altering the location of potassium between these spaces. Dialysate bicarbonates, when elevated, is known to enhance Na^+-K^+-ATPase activity, resulting in the movement of greater amounts of extracellular potassium into the intracellular space, although this process was found not to significantly affect the total amount of potassium removed during dialysis sessions [15]. Confirmation of this came from the study of 35 hemodialyzed patients by Capdevila et al., who examined the effect of changing dialysate bicarbonates on potassium removal during the session. They measured this in each patient's total dialysate from each session, which they collected in a special reservoir. They found that, although these may redistribute potassium (move it intracellularly), they do not prevent its efficient removal by dialysis [14]. This means that plasma alkalization negatively affects potassium removal during the dialysis session.

Plasma tonicity plays a role in the removal of potassium by haemodialysis. Thus, because sodium strongly affects serum and dialysate osmolality, its concentration is a parameter that can be varied to modify the serum tonicity of hemodialyzed patients [16]. Therefore, when it is increased, it is a determining factor in the appearance of hyperkalemia because it causes a redistribution of potassium between the intra- and extra-cellular compartment. Regarding the effect of glucose on tonicity, none of our patients had particularly elevated levels during the study, while the glucose of the dialysate was the same for all dialysis methods used (5.6 mmol/L).

The impact of medicines on the removal of potassium during haemodialysis can also be important. Thus, lack of insulin (diabetes), use of beta-blockers and T_4 were examined to see whether they played a role. In our ten patients, two were diabetics, seven were receiving a selective beta-blocker (metoprolol, bisoprolol, carvedilol), and three were receiving T_4. The reduced amount of insulin (due to diabetes) or lack of glucose (dialysis without

glucose) did not aid the entry of potassium into the cells (our diabetic patients were well regulated and receiving insulin). The action of Na^+-K^+-ATPase is inhibited by the presence of beta-blockers, as they block the action of adrenaline on it, while T_4 enhances it because insufficient regulation of hypothyroidism increases extracellular potassium. However, those receiving T_4 in our study were euthyroid.

From this analysis, it appears that hypertonicity (hyperglycaemia), taking beta-blockers, and insufficient replacement therapy of thyroid function facilitate the elimination of potassium by haemodialysis, since, under these conditions, the Na^+-K^+-ATPase does not operate normally, so potassium is diffused to the outside dominates. From these parameters, in our patients, nothing seems to explain the amount of potassium which is removed, since, among those with the greatest loss of potassium, the one with 336 mmol of potassium in the ultrafiltrate did not have diabetes and was not receiving any medication that affects Na^+-K^+-ATPase, while the patient who lost 255 mmol of potassium per session pre-dilution on-line HDF was also receiving drugs that affecting the pump (beta-blocker and T_4).

An adequate session of conventional haemodialysis can remove the amount of potassium that accumulates in the body during the period between the two sessions. Diffusion accounts for 85% of potassium removal during haemodialysis, and the rate and amount lost are a function of the potassium slope between the serum and dialysate [11,12,17]. That is, the magnitude of the decrease in serum potassium is related to predialysis serum potassium levels [10]. It has been argued that haemodialysis removes potassium from the extracellular space; however, over 60% of the amount removed comes from the intracellular compartment, meaning that the exchange of potassium between these two compartments plays a key role in its removal during the hemodialysis session [18]. The potassium removal in conventional hemodialysis plays a small, but not insignificant, role in its total removal (about 6% of the total amount removed) [19].

Na^+-K^+-ATPase is maximally active in the first hour when hemodialysis is performed with higher serum potassium levels (usually around 4–6 mmol/L). In these conditions, the net efflux of potassium from the intracellular compartment is small and its removal through the filter occurs mainly by elimination of extracellular potassium. Also, when the serum potassium concentration falls below 4 mmol/L, usually after the first 90 min of the dialysis session, its transport from the extracellular to the intracellular space by the Na^+-K^+-ATPase is reduced. As a result, the net efflux of potassium from the intracellular compartment increases due to the existing gradient (via diffusion). In this condition, almost all the potassium removed comes from the intracellular compartment and the serum potassium concentration remains nearly stable [12]. Our study noted that the greatest loss of potassium was found in patients who had a dialysate potassium of 2 mmol/L, which favors the gradient between intracellular and extracellular space (passive diffusion). This observation is important because hemodialysis techniques with potassium profiling have been proposed [20] to combine adequate potassium removal with a reduced risk of malignant arrhythmia in chronic hemodialyzed patients who have an increasing chance of cardiac comorbidities. Care should be taken to ensure adequate potassium removal in patients undergoing hemodialysis who are at risk of cardiac arrhythmias or sudden death.

The removal of a large amount of potassium during the HDF session may not become apparent due to the improvement in blood pH from the entry of bicarbonates into the cells (improvement in acidosis), which, by alkalinizing the blood, moves H^+ from intracellular space and inserts potassium.

While on-line HDF is thought to be more efficient than conventional haemodialysis in the clearance of medium molecular weight molecules, it also improves the clearance of small molecular weight molecules [21] and serum potassium [22]. We found excellent potassium removal in on-line HDF, despite the dialysate supply:blood supply ratio

(500:400 = 1.25) being higher than recommended (1.2), which is thought to maximize potassium removal [23].

However, how is such removal achieved with the on-line HDF? In the post-dilution, our patients received ≥24 L of substitution volume, while, in the pre-dilution, they received ≥48 L. This amount injected into the blood offers a much more alkaline solution to substitute the serum removed with lower bicarbonates. It is obvious that the change in serum pH will affect potassium levels (as it moves potassium intracellularly, in exchange for H^+), even if this movement is not significant, as mentioned before [14,15]. More specifically, a reduction in serum potassium is achieved from the very beginning of the session because, during one hour with post-dilution on-line HDF, around 6 L of substitute are exchanged with 31 or 33 mmol/L of bicarbonates, with serum of a corresponding volume containing a little more than 21.6 mmol/ L of bicarbonates. This provides approximately 60 mmol, which, distributed to the extracellular compartment, increases serum bicarbonates levels by more than 4 mmol/L in a man with 70 kg body weight. These do not have time to be distributed in the intracellular space, since 1.5 to 2 h are required for 25% of the infused amount to move into this space [24,25]. Thus, the function of the Na^+-K^+-ATPase is interrupted, resulting in the diffusion of potassium from the intracellular to the extracellular space and its elimination. This may also explain the greater loss of potassium with pre-dilution on-line HDF, where twice as many liters of substitution fluid are exchanged.

Finally, in our study, potassium removal was excellent in on-line HDF, even though it is mainly diffused and located intracellularly. In fact, we found a huge removal of potassium with pre-dilution on-line HDF (two–three times greater than with conventional haemodialysis found by others) [4], while Meert et al. found that urea and creatinine were more efficiently removed by post-dilution HDF compared to pre-dilution [26]. The very high potassium removed in our opinion is attributed to the large volumes of substitution fluid. By looking at Table 1, one can find that the body water of the patients in our study was less than the substitution volume administered in pre-dilution (>48 L/session) and certainly more than half in post-substitution (>24 L/session).

5. Conclusions

It can be concluded that potassium is much better removed with pre-dilution on-line HDF compared to post-dilution and conventional dialysis and that the filter surface does not play a role. The lower potassium of the dialysate plays an important role in this elimination.

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Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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