Sodium profiling, but not cold dialysate, improves the absolute plasma refill rate during hemodialysis, measured by computer-guided, algorithm-controlled ultrafiltration

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Abstract.
Introduction: In hemodialysis, a discrepancy between ultrafiltration rate (UFR) and plasma refill rate (PRR) often leads to a steep blood volume (BV) decline with ensuing intradialytic hypotension (IDH). Increasing the PRR could reduce IDH. Cold dialysate (CD) stabilizes blood pressure by increasing peripheral vascular resistance and inducing precapillary vasoconstriction. The latter lowers capillary hydrostatic pressure and could therefore also increase the PRR. Sodium profiling (SP) increases the osmolarity in the interstitial compartment. This prevents interstitial fluid volume loss to the intercellular compartment, thereby facilitating refill. Recently, we have developed a method to measure the absolute PRR. Using this method, the effect of CD and SP on refill was investigated.
Methods: Using a Gambro AK200 with BV sensor plus computer-guided external pump, initial UFR was set to 2x linear UFR to achieve a quick preset reduction of blood volume. A software feedback mechanism then continuously adjusted UFR to keep BV constant between very narrow preset boundaries. In this situation, the continuously changing, software-generated UFR quantitatively equalled refill. We measured the absolute PRR in 9 stable patients without IDH, undergoing hemodialysis without intervention, with CD (1 °C below core temperature), and with SP (starting at 150 mmol/l, gradually declining to 140 mmol/l at the end of dialysis).
Results: Baseline PRR was 17.3 ± 5.1 ml/min (mean ± SD). Although CD did not significantly affect the PRR (19.7 ± 5.6 ml/min, NS), SP induced a significant improvement (22.6 ± 7.3 ml/min, p = 0.025 versus baseline). Adding CD to SP did not enhance the effect of SP on refill (n = 3).
Conclusion: Using our new method to measure the absolute plasma refill rate during hemodialysis, we demonstrated that sodium profiling indeed improves the plasma refill rate. A potential effect of cold dialysate on refill could not be established.

Keywords: hemodialysis, computer-guided ultrafiltration, plasma refill rate, cold dialysate, sodium profiling

I. INTRODUCTION

When kidney function is lost, e.g. in end-stage renal disease and acute kidney failure, then fluids, metabolic waste products, and minerals cannot be excreted anymore. The body then loses its ability to maintain proper homeostasis. Without replacement therapy, either peritoneal dialysis or hemodialysis (HD), severe morbidity develops with demise of the patient after a few weeks.

The typical hemodialysis patient is treated 3 to 4 times a week. Blood runs though a dialyzer on the hemodialysis machine. The dialyzer contains a blood and dialysate compartment, separated by a semi-permeable membrane (**Figure 1**). Inside the dialyzer, blood and dialysate flow in countercurrent directions. The chemical differences between blood and dialysate allow substances to diffuse over the semi-permeable membrane. This (partly) restores blood composition. In addition, the dialysate out pump rotates faster than the in pump, creating a negative transmembrane pressure. This pressure causes a fluid flow over the membrane towards the dialysate, a process called ultrafiltration (UF).

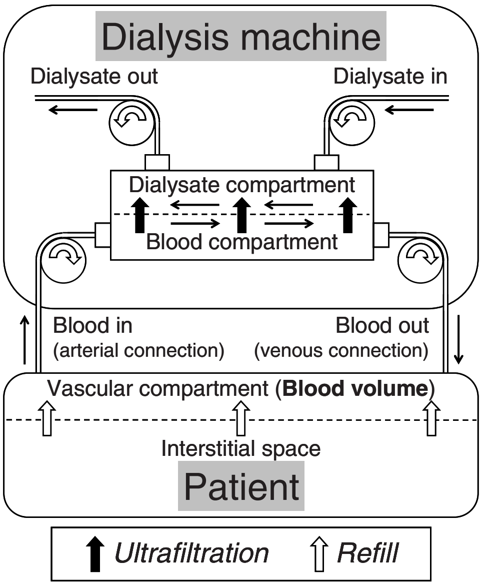

Fig. 1 Schematic overview of the relation between ultrafiltration, plasma refilling, and circulating blood volume during hemodialysis.

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Depending on the patient's fluid intake between treatments, 1 to 4 liters are removed by ultrafiltration per session. This reduces circulating blood volume (BV). Most fluid, however, is accumulated outside the blood in the interstitial space. Blood volume decline causes interstitial fluid to shift towards the circulation (**Figure 1**). As a result, net BV is a function of the hemodialysis machine's ultrafiltration rate (UFR) and internal plasma refill rate (PRR). During treatment, PRR is smaller than the UFR. So, PRR can only partially prevent BV reduction by UFR. Typically, the patient's BV is reduced by 5 to 10 percent at the end of treatment. Reduced BV predisposes to hypotension. Enhancing the PRR with interventions could reduce BV decline, and thus hypotension. However, until recently it was not possible to measure the PRR, making objective assessment of interventions to improve PRR difficult. We developed a method to measure the absolute PRR. The objective of this study was to test this method and to test the influence of interventions that conceivably enhanced refill.

The hypothesis of this study was that during hemodialysis, two interventions (cold dialysate, CD; sodium profiling, SP) would improve the plasma refill rate (PRR) and reduce the number of intradialytic hypotensive episodes (IDH).

The ratio behind this is that fluid transport between the circulation and the interstitial space is dictated by the Starling forces [1] that act at the capillary level. Fluid moves between the capillary and the interstitial space under influence of hydrostatic and oncotic forces in both compartments.

Cold dialysate activates the sympathetic nerve system, causing precapillary vasoconstriction which lowers capillary hydrostatic pressure. This increases the fluid shift towards the capillary and circulation, enhancing the PRR [2].In a similar manner, the increased sodium load of SP increases the plasma and extracellular osmolarity, probably causing intracellular water to shift to the circulation [3], which would enhance refill.

II. MATERIALS AND METHODS

A. Measuring the absolute PRR

A customized system was designed that could measure the absolute PRR [4]. The principle of this method is to control ultrafiltration rate (UFR) with an external system instead of the hemodialysis machine's built-in software. This allowed precise control of UFR, and thus BV. This enables us to keep the BV constant around a preset value.

A hemodialysis machine (Gambro AK200; Gambro AB, Lund, Sweden) with high-flux dialyzer (Fresenius HF80S; Fresenius Medical Care AG, Bad Homburg, Germany) was coupled to an external computer running Poly 5.0 (Inspektor Research Systems, Amsterdam, the Netherlands.) The AK200 contained a blood volume sensor (BVS) that optically measured UF-induced hemoconcentration during hemodialysis, thus enabling measurement of percent blood volume (BV) change. This information was relayed to the computer that controlled an external pump (ISM444, Ismatec Laboratoriumstechnik, GmbH, Wertheim-Mondfeld, Germany). This pump was connected to the dialyzer dialysate compartment. The AK200's ultrafiltration was set to zero.

Table 1 Protocol. BV, blood volume; CD, cold dialysate; HD, hemodialysis; PRR, plasma refill rate; SP, sodium profiling; UFR, ultrafiltration rate

Study	UFR	PRR measurable?	Dialysate sodium (mmol/l)	Temperature (°C)	No. of patients [a]	Aim
1. Standard HD	Constant	-	140	37.0	9	Detect lowest achievable BV reduction without hypotension occurring
2. Baseline	2x UFR (pulse), then computer-guided UF	+	140	37.0	9	Obtain baseline PRR (primary outcome variable), baseline induction phase duration, and induction phase ultrafiltration volume
3. SP	2x UFR (pulse), then computer-guided UF	+	150 → 140 [b]	37.0	9	Investigate the influence of SP on PRR and secondary outcome variables
4. CD	2x UFR (pulse), then computer-guided UF	+	140	1 °C below core T	9	Investigate the influence of CD on PRR and secondary outcome variables
5. SP + CD	2x UFR (pulse), then computer-guided UF	+	150 → 140 [b]	1 °C below core T	3 [c]	Investigate the influence of combined SP and CD on PRR and secondary outcome variables

a. All patients served as their own control

b. Sodium concentration declined exponentially, reaching 145 mmol/l at $t = 0.8 \cdot$ treatment time

c. These patients were part of the group of 9

Table 2 Patient characteristics. ACEi, angiotensin-converting enzyme inhibitor; BB, beta blocker; BMI, body mass index; DryWt, dry weight; HD, hemodialysis; IMN, isosorbide mononitrate

Patient	Primary disease	Sex	Age	DryWt (kg)	BMI (kg/m^2)	Months on HD	Diabetes	Cardiovascular medication	Treatment time (h)
1	Diabetic nephropathy	M	36	92.5	34.0	39	+	ACEi	4
2	Unknown	M	82	78	24.6	11	-	BB, IMN	3
3	Unknown	F	55	77.5	82.5	27	-	-	3
4	Unknown	M	82	63.5	23.9	7	-	ACEi	3
5	Hypertension	M	66	78.5	25.1	7	-	ACEi	3
6	Analgesic induced	F	63	40.5	16.2	16	-	BB	3
7	Unknown	M	77	67	19.8	21	-	IMN	3
8	Hypertension	M	78	72.5	25.1	35	-	-	3
9	Unknown	M	79	75.5	26.1	42	-	IMN	3

The software was programmed to keep the BV within a preset range. This range was defined as either the lowest percent change in BV achieved during standard HD without hypotension plus 2.5%, or the percent change in BV at which hypotension occurred plus 2.5% (**Table 1**; study 1). To measure the PRR, first a strong UF pulse (2 times higher than during standard HD) was given to quickly reach the upper boundary of the preset range. This pulse allowed sufficient time for refill measurements. In addition, it stimulated the initiation of refill. After reaching the upper BV boundary, the computer-guided, algorithm-controlled UF started. This algorithm continuously adjusted pump speed in such a way that BV was kept virtually constant within the pre-defined range. In this situation (constant BV through matching UFR to PRR), the UFR generated by the algorithm quantitatively equals PRR (**Table 1**; study 2).

This method allows direct measurement of the absolute PRR and makes it possible to investigate the effect of interventions on refill (**Table 1**; studies 3-5).

B. Patients

Nine patients were included on the basis of good vascular access and stable weight gain between treatment sessions (**Table 2**). Informed consent was obtained.

C. Measurements

Patient core temperature was measured directly before HD (average value of three measurements) with a FirstTemp Genius tympanic thermometer (Sherwood Medical, Crawley, UK). Blood pressure (BP) before and after HD was measured with an Accutorr Plus BP monitor (Datascope, Paramus, NJ). During HD, BP was determined by an Ohmeda 2300 Finapres BP monitor (BOC Health care, Englewood, CO).

D. Protocol

The study protocol is depicted in **Table 1**. After an initial detection of the lowest achievable BV without hypotension occurring, baseline PRR was determined in a preset BV range. The effects of SP, CD, and a combination of SP and CD were then compared on the basis of:

Primary outcome variable: absolute PRR after the induction phase.

Secondary outcome variables: induction phase volume (ml) and duration (min); BP before, during, and after HD.

E. Statistical analysis

All results are expressed as mean ± SD. All comparisons were performed using SigmaStat version 3.10 (Systat Software Inc., San Jose, CA, 2004). Induction phase duration, induction phase UF volume, and refill were compared between groups using one-way repeated measures analysis of variance (RM-ANOVA) where appropriate followed by a Student-Newman-Keuls (SNK) post hoc test. A $p < 0.05$ was considered significant.

III. RESULTS

A. Absolute PRR

Baseline PRR was 17.3 ± 5.1 ml/min. Sodium profiling induced a significant improvement in refill (22.6 ± 7.3 ml/min, p = 0.025 versus baseline). Cold dialysate did not significantly affect the PRR (19.7 ± 5.6 ml/min, NS). Adding CD to SP did not improve refill (18.4 ± 8.2 ml/min, NS; n=3).

B. Induction phase variables and BP

Baseline induction phase duration was 23.4 ± 15.9 min. Baseline induction phase ultrafiltration volume was 669 ± 477 ml.

In the induction phase, neither the duration nor the total ultrafiltration volume was significantly affected by CD (respectively 24.1 ± 12.5 min and 750 ± 432 ml versus baseline). However, SP increased both variables significantly (respectively 42.3 ± 26.7 min and 1248 ± 850 ml versus baseline). When CD and SP were combined, there was no significant effect (33.3 ± 36.1 min and 959 ± 1236 ml versus baseline).

BP was not changed at all, nor was the frequency of intradialytic hypotensive episodes (data not shown).

IV. DISCUSSION

Sodium profiling and cold dialysate have been reported to prevent intradialytic hypotension [5], presumably in part by enhancing plasma refill rate as explained before. The significantly increased plasma refill rate under sodium profiling (150 → 140 mmol/l) confirms this mechanism. In contrast, we did not find a similar effect for cold dialysate (dialysate temperature 1 ^{o}C below core temperature). The reported beneficial effect of cold dialysate on blood pressure is therefore either a direct effect of vasoconstriction of the large vessels, or our intervention did not induce enough precapillary vasoconstriction. Temperature declined very slowly by 0.5 ± 0.2 ^{o}C (measured at the end of hemodialysis). Further decrease of dialysate temperature could possibly have led to more precapillary vasoconstriction and a significant increase in refill. However, most patients on cold dialysate reported having chills. Therefore, further decrease of dialysate temperature is not an option.

Sodium profiling has the potential to backfire. Increase of the plasma sodium concentration leads to more thirst between hemodialysis sessions. In response, the patient drinks more, increasing the necessary ultrafiltration volume during hemodialysis. This leads to more episodes of intradialytic hypotension [3, 6] making this an intervention with very undesirable side effects.

V. CONCLUSION

Our method allowed measurement of the absolute plasma refill rate during hemodialysis, and investigating the effect of two interventions on refill. Sodium profiling (150 → 140 mmol/l) significantly increased the absolute plasma refill rate, while cold dialysate (1 ^{o}C below core temperature) did not. There was no effect of either intervention on the frequency of intradialytic hypotension.

Our method can be used in further research to study the effect of interventions on refill. In addition, refill most likely reflects the interstitial fluid volume, and thus changes in refill could be used as an accurate marker of dry weight. Further studies are underway to investigate this hypothesis.

VI. REFERENCES

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