Energy Transfer Is the Single Most Important Factor for the Difference in Vascular Response between Isolated Ultrafiltration and Hemodialysis

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Abstract. Differences in vascular reactivity between isolated ultrafiltration (i-UF) and hemodialysis (UF + HD) have been attributed to various factors, including differences in core temperature (CT) and energy transfer (ET). However, the relative importance of these thermal factors is not known. The aim of this study was to elucidate to what extent differences in ET are responsible for the divergent vascular response between i-UF and UF + HD. During four different dialysis treatments in 15 patients, four measurements were performed that consisted of 1 h of i-UF, UF + HD at a dialysate temperature (T_d) of 37.5°C (UF + HD^{37.5}), UF + HD at T_d 35.5°C (UF + HD^{35.5}), and UF + HD with a similar ET as during i-UF(UF + HD^{ET-set}). The UF rate in all sessions was 1 L/h. CT (°C) decreased significantly during i-UF and UF + HD^{ET-set} (P < 0.05), increased significantly during UF + HD^{35.5} (P < 0.05), and remained unchanged during UF + HD^{37.5}. Forearm vascular reactivity increased significantly during i-UF, UF + HD^{ET-set}, and UF + HD^{35.5} (P < 0.05), but not during UF + HD^{37.5} (NS). Venous tone increased significantly during i-UF, UF + HD^{35.5}, and UF + HD^{ET-set} (P < 0.05), and decreased significantly during UF + HD^{37.5} (P < 0.05). When i-UF and UF + HD are matched for ET, all differences in vascular response disappear, showing that differences in ET are the single most important factor for the observed difference in vascular response between i-UF and UF + HD. In contrast to UF + HD^{37.5}, vascular reactivity was improved when the increase in CT was prevented during UF + HD^{35.5} and appeared to increase more when CT was lowered. Preventing the increase in CT during UF + HD appears to be mandatory for optimization of hemodynamic stability during dialysis.

Hypotensive periods are common during hemodialysis, which may lead from minor discomfort to the patient to serious clinical events resulting from myocardial and cerebral ischemia (1). The primary initiating factor for hemodialysis-associated hypotension is a decline in blood volume (2,3). However, arterial and venous reactivity are impaired as well during hemodialysis (4,5). An increase in systemic vascular resistance as well as vasoconstriction, both favoring the return of blood from peripheral vessels to the heart, are of prime importance for the maintenance of hemodynamic stability during a decline in blood volume (6–8). Research of the pathophysiologic mechanisms responsible for the impaired vascular response during hemodialysis has been going on for more than 20 yr. However, until now, the primary responsible factor has not been elucidated. Diffusive removal of vasopressor substances during dialysis has been implicated, as well as changes in electrolyte status or increased nitric oxide production by activated monocytes, stimulated by contact between (contaminated) dialysate and the artificial kidney (9–16). However, none of the above mechanisms was found to be the sole explanatory factor for the reduced vascular reactivity during hemodialysis. Energy transfer (ET) may be an important factor contributing to this phenomenon (17–20). During hemodialysis with standard temperature dialysate (37°C to 38°C), core temperature (CT) increases, which may lead to peripheral vasodilation counteracting the normal vascular response to a decline in blood volume (21). In earlier studies, an improved vascular response was observed during dialysis with cool temperature dialysate (35°C to 36°C) and isolated ultrafiltration (i-UF) compared with standard temperature dialysate (22,23).

CT generally remains stable during cool dialysis and decreases during i-UF due to pronounced energy loss from the patient to the extracorporeal circuit (24). Thermal factors may therefore be of great importance in this respect. However, until now, it is not known to what extent differences in extracorporeal energy transfer (ET) or changes in CT are responsible for the divergent vascular response between i-UF and hemodialysis.

New techniques enable us to measure CT and ET during i-UF and dialysis, and to model exactly the desired amount of ET during a dialysis session (17,18,25). The aim of the present study was to assess whether differences in vascular response between i-UF and hemodialysis combined with ultrafiltration...
(UF + HD) are primarily caused by differences in extracorporeal ET between these techniques. Furthermore, we wanted to know whether the CT should be lowered or whether it is sufficient to prevent the increase in CT during dialysis to obtain an optimal vascular response.

Materials and Methods

Study Population

Fifteen patients (8 women, 7 men) were selected from the chronic hemodialysis population from the Kuratorium für Dialyse und Nierentransplantation in Würselen, Germany. The patient group had a mean age of 55 yr (range, 21 to 77) and an average time on renal replacement therapy of 43.9 mo (range, 4 to 252). Renal disease was caused by chronic glomerulonephritis (n = 2), hypertensive nephrosclerosis (n = 5), nephrolithiasis (n = 1), reflux nephropathy (n = 3), juvenile nephronophthisis (n = 1), rapidly progressive glomerulonephritis (n = 2), and analgetic nephropathy (n = 1). Dialysis patients with diabetes mellitus, severe coronary heart disease (New York Heart Association classifications II or more), and a compromised left venous drainage (nephritis (n = 5), nephrolithiasis (n = 3), reflux nephropathy (n = 3), juvenile nephronophthisis (n = 1), rapidly progressive glomerulonephritis (n = 2), and analgetic nephropathy (n = 1). Dialysis patients with diabetes mellitus, severe coronary heart disease (New York Heart Association classifications II or more), and a compromised left venous drainage were excluded from the study for ethical reasons, as they were believed to be more prone to hypotensive periods with an increased CT at a higher dialysate temperature (Tc) (26–33). The following antihypertensive medications were used by the patients: angiotensin-converting enzyme inhibitors (n = 4), β-blocking agents (n = 8), calcium channel blocking agents (n = 7), diuretics (n = 5), angiotensin II receptor antagonists (n = 3), and α-blocking agents (n = 3).

All medication was continued to study daily clinical practice in the treatment of dialysis patients who were dependent on antihypertensive medication. The patients also received their medication on the day of treatment of dialysis patients who were dependent on antihypertensive medication. The patients also received their medication on the day of treatment.

Study Design

The study consisted of four sessions each of 1 h of i-UF, UF + HD at a Tc of 37.5°C (UF + HD37.5°C), UF + HD at a Tc of 35.5°C (UF + HD35.5°C), and UF + HD in which the ET was similar (UF + HDET-set) for that particular patient as during i-UF. A dialysate temperature of 35.5°C was chosen because previous studies showed that CT remained unchanged with this temperature (20,22,23). The sessions were performed in a random order. The UF rate in all sessions was 1 L during the first hour. All measurements started at the beginning of the dialysis session. Each patient served as his or her own control, and measurements were done on the same day of the week for each patient, thus eliminating as much bias as possible. The study was performed during 1 h to prevent too large a decrease in CT during i-UF and UF + HDET-set. We showed recently that the ET and CT during i-UF reached a stable level within 15 min after the start of the treatment (20,24). Furthermore, earlier studies already showed a large difference in vascular reactivity between UF + HD37.5°C, UF + HD35.5°C, and i-UF 15 min after the start of the treatment (4,5,16,23).

During all measurement sessions and during UF + HDET-set CT, the temperature at the arterial (Tart) and venous (Tven) side of the fistula, the ET between the extracorporeal circuit and the patient, and the Tc were monitored at 10-s intervals using the method described below.

Energy Transfer

ET was defined as the amount of thermal energy that was transferred from the extracorporeal circuit to the patient or vice versa. A positive value indicates net energy gain from the extracorporeal circuit to the patient, and a negative value indicates net energy loss from the patient to the extracorporeal circuit. Tart and Tven were assessed by use of continuous blood temperature monitoring (BTM®, Fresenius Medical Care, Den Bosch, The Netherlands) at the arterial and venous side of the extracorporeal system by an air-filled head with a platinum sensor fitted around the arterial and venous catheters. By measuring Tart and Tven, ET can be calculated according to the following formula: c × ρ × Qb × (Tven − Tart) × t, where c is specific thermal capacity (3.64 kJ/kg °C), Qb is extracorporeal blood flow, ρ is the density of blood (1052 kg/m³), and t is dialysis time (in hours) (34).

The BTM not only can passively calculate, but also can actively model the ET in the extracorporeal circuit. The rate at which thermal energy is to be fed or withdrawn from the patient via the extracorporeal circuit is achieved automatically by the thermal flux option of the BTM, which measures Tart, Tven, and Qb in 15-s intervals and which actually calculates the actual ET according to the above-mentioned equation. The information of the actual ET is used by the algorithm of the BTM to automatically set and continuously adjust the Tc to reach and maintain the target CT. The ET rate is expressed in Watts (1 Watt = 3.6 kJ/h).

Core Temperature

The CT was measured by using the BTM described above. The BTM measures the temperature at the arterial side of the fistula and calculates central venous blood temperature by correcting for fistula and cardiopulmonary recirculation. This temperature is referred to as CT. This correction is necessary because the arterial blood temperature is determined by the CT as well as by the temperature of the recirculated venous blood. Recirculation is measured by the BTM with a temperature bolus, which is produced by a temporary change in Tc. The change in temperature is recorded by the venous sensor head of the BTM and finally by the arterial sensor head. From the ratio in bolus sizes, recirculation can be calculated (18). Predialytic CT is defined as the first reliable temperature obtained (in all patients within 5 min) after the start of dialysis. The accuracy of the CT is less than 0.1°C as given by the manufacturer (Fresenius Medical Care). By using the display of the BTM, it is possible to read the instantaneous Tc. The treatment session would be terminated when CT dropped more than 1.0°C, Tc went below 34.0°C, or the patient experienced severe cold or shivers.

Vascular Reactivity

Systolic BP (SBP), diastolic BP (DBP), mean arterial BP (MAP), and heart rate (HR) were measured with the Finapres method (Finapres, Ohmeda 2300; Lameris, The Netherlands). The mean value of 3 min was calculated. With the Finapres device, MAP and HR were measured beat to beat at zero transmural pressure by the use of a small finger cuff that is equipped with an infrared photoplethysmograph (35). The Finapres cuff was applied to the third finger. Vascular reactivity was studied at the nonfistula arm, which was positioned just above heart level using strain-gauge plethysmography as described by Whitney (Periflow; Janssen Scientific Instruments, Beere, Belgium) (36). An inflatable cuff was applied to the upper arm while the mercury-filled strain gauge was positioned at the thickest part of the forearm. In addition, an antecubital vein was cannulated (Venflon, 1 mm diameter) for the recording of direct intravenous pressure (Hewlett-Packard 7820SC pressure monitor). Venous tone (VT, mmHg/ml per 100 ml) (pressure/volume ratio pointing to active venous constriction) and forearm vascular resistance (FVR, mmHg/ml per 100 ml per min) were measured as described previously by van
Kuijk et al. (22). The coefficient of variation of consecutive measurements is 11.9% (8).

Blood Volume
Changes in relative blood volume (BV) were measured continuously and noninvasively by means of an optical reflection method, which measures the absorption and scattering properties of red blood cells as they pass through the hemodialysis circuit (Crit-line; In-Line Diagnostics, Riverdale, UT). The optical sensor was clipped to the in-line blood chamber on the arterial line, and trends of hematocrit and %BV (versus time) were logged over the entire treatment period. In previous studies, it has been shown that relative changes in BV can reliably be determined during hemodialysis by the serial monitoring of hematocrit (37–39). The baseline value was obtained after 2 min of extracorporeal circulation at a blood flow of 250 ml/min without ultrafiltration to exclude the influence of saline (recirculation) present in the extracorporeal circuit at the start of dialysis.

Dialysis Prescription
During each of the four treatment sessions, blood flow ($Q_b$), dialysate flow ($Q_d$), and dialysate composition were the same. The composition of the dialysate was: 28 mmol/L to 36 mmol/L bicarbonate, 136 mmol/L to 140 mmol/L sodium, 1.75 mmol/L calcium, 3 mmol/L acetate, 1 mmol/L to 3 mmol/L potassium, 0.5 mmol/L magnesium, and 108 mmol/L chloride. The membranes used in our study were as follows: a polysulfone membrane (F60S; Fresenius, Bad Homburg, Germany) in two patients, an excebrane membrane (E15; Terumo, Leuven, Belgium) in two patients, and a cellulose membrane (S12; Terumo) in 11 patients. Room temperature was kept constant between 22 and 23°C by climate control.

Statistical Analyses
Comparison between the values before the start and after 1 h of treatment within each treatment, as well as changes in predialysis weight, interdialytic weight gain, blood volume, CT, ET, and vascular reactivity (FVR and VT) between the different treatments were analyzed by Friedman ANOVA and, if appropriate, by the Wilcoxon signed rank test (Statistical Package for the Social Sciences PC version 7.5) (40). A $P$ value <0.05 was considered significant. Data are expressed as mean ± SD.

Results
The predialysis weight in the four treatment sessions (i-UF, UF + HD$^{37.5}$, UF + HD$^{35.5}$, and UF + HD$^{ET-SET}$) was, respectively, 73.78 ± 17.15, 73.95 ± 17.31, 74.15 ± 17.55, and 74.45 ± 17.61 kg (NS). The interdialytic weight gain was 2.54 ± 0.81, 2.74 ± 0.95, 2.77 ± 1.14, and 3.02 ± 1.23 kg in the four treatment sessions (NS).

Changes in Energy Transfer
ET (Figure 1) decreased significantly during i-UF, UF + HD$^{ET-SET}$, and UF + HD$^{35.5}$ ($P < 0.05$), and remained unchanged during UF + HD$^{37.5}$ (NS). Between i-UF and UF + HD$^{ET-SET}$, the difference in ET was not significant, whereas in all other possible combinations of treatments, the change in ET was significant ($P < 0.05$). To reach the same energy transfer during UF + HD$^{ET-SET}$ as during i-UF, the $T_d$ had to be decreased to a mean $T_d$ of 34.47 ± 0.71°C (range, 33.61 to 36.0°C).

Changes in Core Temperature
The predialysis CT in the four treatment sessions (i-UF, UF + HD$^{37.5}$, UF + HD$^{35.5}$, and UF + HD$^{ET-SET}$) was, respectively, 36.44 ± 0.39, 36.54 ± 0.31, 36.42 ± 0.35, and 36.53 ± 0.37°C (NS). Changes in CT are shown in Figure [fgc + 1]1. CT decreased significantly during i-UF and UF + HD$^{ET-SET}$ ($P < 0.05$), increased significantly during UF + HD$^{37.5}$ ($P < 0.05$), and remained unchanged during UF + HD$^{35.5}$ (NS). Between i-UF and UF + HD$^{37.5}$, i-UF and UF + HD$^{ET-SET}$, i-UF and UF + HD$^{35.5}$, UF + HD$^{37.5}$ and UF + HD$^{ET-SET}$, UF

* $P < 0.05$, changes versus baseline.
+ HD$^{37.5}$ and UF + HD$^{35.5}$ and UF + HD$^{ET\text{-set}}$, changes in CT were significant ($P < 0.05$).

**Changes in Blood Volume**

The decrease in blood volume versus baseline in the four treatment sessions (i-UF, UF + HD$^{37.5}$, UF + HD$^{35.5}$, and UF + HD$^{ET\text{-set}}$) was, respectively, $-5.79 \pm 3.96\%$ ($P < 0.05$), $-7.23 \pm 5.55\%$ ($P < 0.05$), $-5.75 \pm 3.12\%$ ($P < 0.05$), and $-7.14 \pm 4.98\%$ ($P < 0.05$). In the four treatment sessions, there were no significant differences (NS).

**Changes in Vascular Reactivity**

FVR increased significantly during i-UF, UF + HD$^{ET\text{-set}}$ and UF + HD$^{35.5}$ ($P < 0.05$), but not during UF + HD$^{37.5}$ (NS) (Figure 2). Between i-UF and UF + HD$^{37.5}$, UF + HD$^{ET\text{-set}}$ and UF + HD$^{37.5}$, and UF + HD$^{35.5}$ and UF + HD$^{37.5}$, the change in FVR was significant ($P < 0.05$), whereas in all other possible combinations there were no significant differences.

VT increased significantly during i-UF, UF + HD$^{ET\text{-set}}$, and UF + HD$^{35.5}$ ($P < 0.05$), and decreased significantly during UF + HD$^{37.5}$ ($P < 0.05$) (Figure [fgc + 2][2]). Between i-UF and UF + HD$^{37.5}$, UF + HD$^{35.5}$ and UF + HD$^{37.5}$, and UF + HD$^{ET\text{-set}}$ and UF + HD$^{37.5}$, the change in VT was significant ($P < 0.05$).

**Changes in BP**

SBP, DBP, and MAP decreased significantly during UF + HD$^{37.5}$ ($P < 0.05$) and remained unchanged in the other three treatment sessions (Table 1). There were no significant differences in changes in SBP, DBP, and MAP in the four treatment sessions.

**Side Effects**

In one patient who experienced chills, $T_d$ decreased to 33.61°C during UF + HD$^{ET\text{-set}}$. Because a $T_d$ of 34.0°C was considered the lowest threshold value, ET was changed to a slightly less negative value. There were no other intradialytic symptoms.

**Discussion**

Our study is the first to show that the difference in vascular reactivity between i-UF and hemodialysis disappears when both treatment modalities are matched for extracorporeal ET, suggesting that this is the single most important factor for the divergent vascular response between i-UF and UF-HD.

During UF + HD$^{37.5}$, CT increased, whereas during i-UF and UF + HD$^{ET\text{-set}}$, CT decreased, and during UF + HD$^{35.5}$, CT remained unchanged. These changes in CT are in accordance with previous studies (17,20,41,42). In this and in earlier studies, the increase in CT during UF + HD$^{37.5}$ occurred in the absence of heat transfer from the extracorporeal circuit to the patient, suggesting that the dialysis treatment itself has an effect on CT regulation (20,41). This would also explain the fact that the decrease in CT was more pronounced during i-UF compared with UF + HD$^{ET\text{-set}}$. The potential mechanisms behind this phenomenon remain to be elucidated. Possible explanations have been discussed previously and include the production of a CT increasing factor derived from contact with a bioincompatible membrane or “unpure” dialysate, or the removal of a CT decreasing factor during dialysis (42– 44). It has also been hypothesized that peripheral vasoconstriction during a decline in BV results in reduced heat loss from the skin, and therefore in an increase in CT (24). However, the fact that in this and earlier studies only minor changes in FVR and VT were observed during UF + HD$^{37.5}$ would argue against this hypothesis (16,22).

![Figure 2. Changes in forearm vascular resistance and venous tone. Boxes indicate the 25th to 75th percentile range, and capped bars indicate the 10th to 90th percentile range. Median (thick horizontal lines) i-UF is isolated ultrafiltration; UF + HD$^{37.5}$ is ultrafiltration combined with hemodialysis at a dialysate temperature of 37.5°C; UF + HD$^{35.5}$ is ultrafiltration combined with hemodialysis at a dialysate temperature of 35.5°C; UF + HD$^{ET\text{-set}}$ is ultrafiltration combined with hemodialysis in which the ET was similar for that particular patient as during i-UF. *$P < 0.05$, changes versus baseline.](image-url)
The $T_d$ decreased to a mean value of 34.47°C during 1 h of UF + HD$_{ET}$-set, which is in accordance with the results from our previous study (20). Unpublished results of the latter study showed that when UF + HD$_{ET}$-set was continued during a full dialysis session, $T_d$ and CT did not decrease any further after the first hour.

Regarding the hemodynamic response, FVR did not increase significantly during UF + HD$_{37.5}$, in contrast to the other treatment modalities. This strongly suggests that the increase in CT during UF + HD$_{37.5}$ is the most important factor for the impaired vascular response during UF-HD. This could be explained by a conflict between thermal regulatory mechanisms, favoring peripheral vasodilation to lose excess heat, and circulatory homeostatic mechanisms favoring vasoconstriction (7,21,45,46). Indeed, the increase in FVR was significantly higher when the increase in CT was prevented during UF + HD$_{37.5}$. The increase in FVR even appeared to be more pronounced with the further lowering of CT during i-UF and UF + HD$_{ET}$-set, although the difference was not statistically significant. Regarding the reactivity of the venous system, VT even decreased during UF + HD$_{37.5}$, suggesting that the peripheral venous system even appears to be more susceptible for changes in CT. It has indeed been shown in earlier studies that during an increase in CT, venodilation precedes arteriolar dilation (47). The effect of UF + HD on the venous system is possibly of great clinical importance, because the centralization of blood from the peripheral compartment during a decline in blood volume is partly mediated by changes in VT (8,48).

During UF + HD$_{37.5}$, MAP decreased significantly versus baseline, whereas during the other treatments, there were no significant differences, which is in accordance with the directly measured changes in FVR and VT.

It is concluded that differences in vascular response between i-UF and UF + HD disappear when treatment modalities are matched for the extracorporeal ET, suggesting that this is the single most important factor for the divergent vascular response between UF + HD and i-UF. Prevention of the increase in CT during hemodialysis significantly improves the constriction of the peripheral resistance and capacitance vessels, although vascular reactivity even appeared to be somewhat more pronounced with a further lowering of CT. Prevention of the increase in CT by adjusting the dialysate temperature during UF + HD appears to be mandatory for the optimization of hemodynamic stability during dialysis. This might be even more clinical importance in the treatment of hypotensive-prone cardiac-compromised patients.

### References

12. Bergamo Collaborative Dialysis Study Group: Acute intradial-

### Table 1. Blood pressure parameters

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
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</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>i-UF</td>
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<td>139 (28)</td>
<td>72 (17)</td>
</tr>
<tr>
<td>UF + HD$_{35.5}$</td>
<td>144 (24)</td>
<td>144 (26)</td>
<td>68 (14)</td>
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<tr>
<td>UF + HD$_{37.5}$</td>
<td>152 (22)</td>
<td>134 (23)$^b$</td>
<td>75 (9)</td>
</tr>
<tr>
<td>UF + HD$_{ET}$-set</td>
<td>144 (23)</td>
<td>141 (28)</td>
<td>73 (14)</td>
</tr>
</tbody>
</table>

$^a$ Data are expressed as mean (SD). SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; Before, at the start of the measurement; After, at the end of the measurement; i-UF, isolated ultrafiltration; UF + HD$_{35.5}$, ultrafiltration combined with hemodialysis at a dialysate temperature of 37.5°C; UF + HD$_{37.5}$, ultrafiltration combined with hemodialysis at a dialysate temperature of 35.5°C; UF + HD$_{ET}$-set, ultrafiltration combined with hemodialysis in which the ET was similar for that particular patient as during i-UF.

$^b$ P < 0.05, after versus before.
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