Critical Role of the Extracorporeal Blood Temperature in the Hemodynamic Response During Hemofiltration

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Abstract. Impaired vascular reactivity during combined ultrafiltration-hemodialysis (UF + HD) compared with hemofiltration (HF) remains a rather enigmatic problem, the causes of which are still not well understood. Although a number of factors have been claimed to be responsible, most recent studies point to a major role of the extracorporeal blood temperature, which is usually lower during HF compared with UF + HD. However, previous studies in which hemodynamics were studied during UF + HD and HF in relation to the extracorporeal blood temperature are limited by the use of acetate in UF + HD, and measurements were often confined to BP and heart rate. Therefore, arterial BP, as well as forearm vascular resistance (FVR) and venous tone (strain-gauge plethysmography), was measured in 11 hemodialysis patients during 3 h UF + HD (37.5°C) and predilution HF (39.0°C = warm HF), resulting in equivalent extracorporeal blood temperatures. Patients were also studied during cold HF at an infusate temperature of 36.0°C. UF + HD and HF were matched with respect to the dialysate and infusate composition (bicarbonate), bio-compatibility factors, and small molecule clearance. At equivalent temperatures, UF + HD and HF were associated with a comparable vascular and BP response. Only cold HF was associated with a significant increase in FVR. In addition, FVR and venous tone, as well as arterial BP, were all significantly higher during cold HF compared with both UF + HD and warm HF. These results indicate that the disparity in vascular reactivity between UF + HD and HF is primarily related to differences in the extracorporeal blood temperature.

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With an increasing number of elderly, cardiovascular compromised patients on dialysis therapy, hemodynamic instability with symptomatic hypotension will remain an important clinical problem. Since their clinical application, convective dialysis treatments such as hemofiltration (HF) are considered the most optimal treatment modality for hemodynamically unstable patients because BP stability is better during these treatments compared with diffusive treatments such as combined ultrafiltration-hemodialysis (UF + HD) (1). Previous studies have shown that these differences in BP stability are mainly related to the fact that peripheral vascular resistance increases adequately during HF, whereas peripheral vascular resistance remains more or less unchanged during UF + HD (2,3). In addition, we found that venous reactivity is also impaired during the latter therapy (4). Although HF seems to be the most optimal treatment for cardiovascular compromised patients, its clinical application is still limited due to the higher cost and limitations in clearance with higher hematocrits as result of the use of erythropoietin. If we can identify the mechanisms responsible for disparity in vascular reactivity between convective and diffusive dialysis treatments, it should be possible to improve hemodynamic stability during the latter treatment modality.

Traditionally, the larger decrease in plasma osmolality as result of a larger small molecule clearance was thought to play a pivotal role in the impaired vascular response during UF + HD (5). However, urea-supplemented dialysate did not improve the hemodynamic response in dogs and men (6,7). Moreover, we found a comparable vascular response during high and low sodium dialysis (8). Henderson et al. suggested that the impaired vascular response during UF + HD might be related to bioincompatibility factors related to the dialysate membrane or to the presence of nonsterile dialysate (9). However, vascular reactivity was not improved during UF + HD when using sterile dialysate, whereas Aakhus et al. measured comparable central hemodynamics using membranes of low and high biocompatibility (10,11).

A third factor that could explain the improved vascular response during HF concerns the extracorporeal blood temperature, which is usually lower during this treatment compared with UF + HD. In several studies it was found that hemodynamic stability could be improved during UF + HD by lowering the dialysate temperature (12–14). However, studies that actually compared UF + HD with HF are often confounded by the use of acetate as a single buffer in UF + HD, whereas hemodynamics and changes in blood volume were not always monitored (15). In another study, the extracorporeal blood temperatures were probably not completely matched (16).
Therefore, we measured arterial BP, as well as vascular reactivity, under strictly standardized conditions in relation to the extracorporeal blood temperature comparing UF + HD with predilution HF. In both treatments, bicarbonate was used as a buffer.

Materials and Methods

Patients and Dialysis

After obtaining informed consent, four women and seven men on intermittent hemodialysis with a mean age of 43 yr (range, 26 to 58) and a mean time on dialysis of 65 mo (range, 5 to 252) were included. All of the participants were hemodynamically stable patients who rarely (in <10% of their dialysis encounters) suffered from intradialytic hypotension (defined as the requirement of volume expansion therapy due to either a systolic BP < 95 mmHg, a decrease in systolic BP of > 20 mmHg, or the presence of symptoms such as cramping, nausea, or vomiting). The following exclusion criteria were used: (1) severe coronary (New York Heart Association classification II or more) or valvular heart disease; (2) compromised left ventricular function (ejection fraction ≤ 30%); and (3) diabetes mellitus. By adjusting fluid intake, patients were instructed to achieve a pre-dialysis weight in the range of 2.0 to 3.0 kg above their dry weight that was estimated by echography of the inferior caval vein (17). Vasoactive medication was stopped 48 h before the study, and patients were not allowed to drink caffeine-containing beverages during the last 12 h before the study. Recirculation was <10% in the studied population.

With each patient serving as his or her own control, measurements were performed during three consecutive dialysis treatments in a random order. Blood flow was set at 300 ml/min in all treatments while the same ultrafiltration rate was used within the same patient. One session consisted of 3 h of UF + HD, using a polyamide dialyzer (Polyflux 160; Gambro, Lund, Sweden), and a dialysate flow of 500 ml/min. The dialysate temperature was set at 37.5°C, which in our experience resulted in a comparable arterial and venous blood temperature (see Methods) at the start of dialysis indicative of the absence of either heat load or loss at the dialyzer level. The other two sessions consisted of 3 h predilution HF, using a polyamide hemofilter (FH 88 H, Gambro), and an infusate flow of 350 ml/min to obtain an almost comparable small molecule clearance as in UF + HD. In one session, the infusate temperature was set at 39.0°C (warm HF) to obtain the same blood temperature in the efferent venous line as during UF + HD. On the basis of former experiments, the infusate temperature was set at 36.0°C in cold HF to obtain a comparable extracorporeal blood temperature as in postdilution HF.

UF + HD and HF were performed with an AK-100 Ultra monitor (Gambro) to prepare on-line sterile infusate and dialysate. The composition of both dialysate and infusate was (in mmol/L): 141 sodium, 2.0 potassium, 1.75 calcium, 34 bicarbonate, 3 acetate, 0.5 magnesium, and 108 chloride.

Methods

After inserting the dialysis needles, patients were in supine rest for 30 min. The luminal blood temperature was measured in the arterial and venous line with needle thermometers (78214C temperature monitor, Hewlett-Packard, Avondale, PA). Connectors with a built-in adaptor were placed in the arterial and venous line under sterile conditions at a distance of approximately 15 cm from the patient. There was no direct contact between blood and thermometer.

All hemodynamic measurements were performed before (pretreatment) and every 30 min during dialysis. Using strain-gauge plethysmography, forearm vascular reactivity was assessed at the nonfistula arm that was positioned just above heart level (Periflow; Janssen Scientific Instruments, Turnhout, Belgium) (18). A 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; Ohmeda AB, Helsingborg, Sweden) for the recording of direct intravenous pressure (Hewlett-Packard 78205C pressure monitor).

Changes in venous tone (VT) (active venous constriction) were estimated by recording the pressure/volume ratio (mmHg/ml per 100 ml) at a cuff pressure of 40 mmHg (19). Pressure was applied until both intravenous pressure and arm volume had reached a plateau. Pressure and volume were estimated directly after the deflation of the upper arm cuff to minimize the influence of capillary filtration on assessing volume. To measure forearm blood flow, the upper arm cuff was rapidly inflated 5 s after the R-wave of the electrocardiogram at a cuff pressure of 50 mmHg. The inflation/deflation ratio was 3:2 heart beats. The hand circulation was occluded from 1 min previous, as well as during flow measurements. Forearm blood flow was estimated using a computerized integrator. Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure by forearm blood flow (mmHg/ml/100 ml/s). BP was measured with an automatic BP monitor (Dinamap 1486 SX; Critikon Inc., Tampa, FL). The average of four consecutive measurements was recorded. Continuous heart rate was derived from an electrocardiogram.

Changes in relative blood volume were measured continuously and noninvasively by means of an optical reflection method that operates at a wavelength of 950 nm. The optical sensor was clipped on the arterial line (Haemoguard 2000; Sanofi Sante, Maasslius, The Netherlands) (20). The baseline value was obtained after 2 min of extracorporeal circulation at a blood flow rate of 250 ml/min without ultrafiltration to exclude the influence of saline (recirculation) present in the blood lines at the start of dialysis.

Both before and after dialysis, blood was withdrawn for the estimation of sodium, potassium, ionized calcium (NOVA 8, NOVA Biomedical, Waltham, MA), total CO2, urea, osmolality (vapor pressure monitor; Wescor, Logan, UT), and colloid osmotic pressure. In addition, blood was withdrawn in ice-chilled tubes and directly centrifuged at a temperature of 4°C for the estimation of plasma catecholamines (HPLC, fluorescence detection).

Statistical Analyses

Changes in hemodynamic parameters within each treatment, as well as differences between treatments, were analyzed by repeated multivariate ANOVA (Statistical Package for the Social Sciences, PC version). If the sphericity of the variance-covariance matrix appeared to be violated, degrees of freedom in the univariate multivariate ANOVA tests were corrected by the Greenhouse-Geisser epsilon to avoid type I error in testing the F ratio. All laboratory parameters were analyzed by Friedman’s ANOVA and, if appropriate, by the Wilcoxon’s signed-rank test. All values are expressed as mean ± SD.

Results

The predialysis weights in UF + HD, warm HF, and cold HF were 69.2 ± 10.8, 69.3 ± 11.1, and 69.5 ± 10.9 kg (NS), respectively, whereas the mean ultrafiltration rate was 0.92 ± 0.12 L/h. The postdialysis weights were 66.3 ± 10.9, 66.4 ± 10.9, and 66.7 ± 10.8 (NS), respectively. The blood temperatures are shown in Figure 1, A through C. UF + HD and warm F were associated with an almost comparable arterial and venous blood temperature. After 3 h, the arterial blood tem-
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Figure 1. (A) Arterial (----) and venous (- - -) blood temperatures in UF + HD. *, $P < 0.01$; #, $P < 0.05$ compared with $t = 0$ min. (B) Arterial (----) and venous (- - -) blood temperatures in warm HF. *, $P < 0.01$ compared with $t = 0$ min. (C) Arterial (----) and venous (- - -) blood temperatures in cold HF. *, $P < 0.05$ compared with $t = 0$ min.

Temperature increased by $0.4 \pm 0.2^\circ C$ in both treatments ($P < 0.01$). In addition, the venous blood temperature increased by $0.2 \pm 0.2 (P < 0.05)$ and $0.3 \pm 0.2^\circ C (P < 0.01)$, respectively. In cold HF, blood cooled down during extracorporeal circulation by $1.2^\circ C$, whereas after 3 h the arterial blood temperature had increased by $0.1 \pm 0.2^\circ C (P < 0.05)$ without significant changes in the venous blood temperature. Differences in arterial blood temperature between the three treatment modalities at the start of dialysis did not reach statistical significance.

The laboratory data are shown in Table 1. All laboratory
Table 1. Laboratory data

<table>
<thead>
<tr>
<th>Category</th>
<th>HD 37.5°C</th>
<th>HF 39.0°C</th>
<th>HF 36.0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>139.0 (2.1)</td>
<td>140.1 (2.1)b</td>
<td>137.4 (2.5)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.7 (0.6)</td>
<td>3.5 (0.4)b</td>
<td>4.7 (0.5)</td>
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<tr>
<td>Ionized calcium (mol/L)</td>
<td>1.17 (0.13)</td>
<td>1.40 (0.08)b</td>
<td>1.14 (0.13)</td>
</tr>
<tr>
<td>Total CO₂ (mmol/L)</td>
<td>22.7 (2.8)</td>
<td>25.6 (1.4)b</td>
<td>23.1 (3.2)</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>25.0 (7.3)</td>
<td>9.7 (3.5)b</td>
<td>25.9 (6.5)</td>
</tr>
<tr>
<td>URR (%)</td>
<td>59.5 (15.9)</td>
<td>59.5 (15.9)</td>
<td>53.5 (10.4)</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg)</td>
<td>295.3 (7.7)</td>
<td>283.2 (5.6)b</td>
<td>297.4 (7.3)</td>
</tr>
<tr>
<td>COP (kPa)</td>
<td>2.9 (0.3)</td>
<td>4.4 (0.4)b</td>
<td>2.9 (0.3)</td>
</tr>
<tr>
<td>Noradrenaline (nmol/L)</td>
<td>1.27 (0.47)</td>
<td>1.58 (0.51)</td>
<td>1.10 (0.87)</td>
</tr>
<tr>
<td>Adrenaline (nmol/L)</td>
<td>0.12 (0.11)</td>
<td>0.13 (0.10)</td>
<td>0.15 (0.12)</td>
</tr>
</tbody>
</table>

*a HD, hemodialysis; HF, hemofiltration; URR, urea reduction ratio; COP, colloid oncotic pressure.

*b P < 0.01, postdilution versus predilution.

*c P < 0.05, postdilution versus predilution.

parameters changed comparably during the different treatment modalities. The decrease in plasma potassium, urea, and osmolality and the increase in total CO₂ tended to be smaller during both warm and cold HF compared with UF + HD, but these differences did not reach statistical significance. In addition, differences in the urea reduction ratio were not statistically significant. There were no significant changes in plasma adrenaline or noradrenaline. Relative blood volume decreased significantly (P < 0.01) and comparably to 86 ± 6, 84 ± 6, and 85 ± 6%, respectively, during UF + HD, warm HF, and cold HF.

The hemodynamic data are presented in Table 2 and in Figure 2, A through C. UF + HD and warm HF were associated with comparable vascular and BP responses, with no significant differences between the two treatments. In both, FVR tended to increase during the first hour (P > 0.05), after which it stabilized, whereas VT decreased significantly. In contrast, cold HF was associated with a significant increase in FVR, especially during the first 2 h, whereas VT remained unchanged. Compared with both UF + HD and warm HF, FVR (P < 0.01) and VT (P < 0.05) were significantly higher during cold HF. There were no significant changes in arterial BP during UF + HD. During warm HF, only systolic BP decreased significantly, whereas heart rate increased significantly during both UF + HD and warm HF. In cold HF, all three BP parameters increased significantly, whereas heart rate decreased. Mean arterial BP was significantly higher compared with both UF + HD and warm HF (P < 0.05). Differences in systolic (P < 0.05) and diastolic (P < 0.05) BP reached statistical significance only between warm and cold HF.

Discussion

The results presented here show that under standardized conditions and at equivalent extracorporeal blood temperatures the vascular and BP responses are comparable between UF + HD and HF. Only with extracorporeal blood cooling is HF associated with an increase in peripheral resistance and a more stable VT, resulting in a higher BP.

In our experience, both pre- and postdilution HF are associated with a lower extracorporeal blood temperature compared

Table 2. Hemodynamic data

<table>
<thead>
<tr>
<th>Category</th>
<th>HD 37.5°C</th>
<th>HF 39.0°C</th>
<th>HF 36.0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>129 (17)</td>
<td>126 (25)</td>
<td>133 (20)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77 (9)</td>
<td>80 (10)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>Mean arterial BP (mm Hg)</td>
<td>97 (12)</td>
<td>98 (17)</td>
<td>101 (15)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 (7)</td>
<td>78 (16)c</td>
<td>70 (6)</td>
</tr>
<tr>
<td>FVR (mm Hg/ml/100 ml/s)</td>
<td>1524 (606)</td>
<td>2186 (2318)</td>
<td>1704 (664)</td>
</tr>
<tr>
<td>VT (mm Hg/ml/100 ml)</td>
<td>18.5 (5.2)</td>
<td>15.7 (5.0)b</td>
<td>19.2 (3.3)</td>
</tr>
</tbody>
</table>

*a FVR, forearm vascular resistance; VT, venous tone.

*b P < 0.01, postdilution versus predilution.

*c P < 0.05, postdilution versus predilution.
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Figure 2. (A) Systolic, mean arterial, and diastolic BP during UF + HD (---), warm HF (---), and cold HF (· · ·). *, *P < 0.01 compared with pretreatment level. (B) FVR during UF + HD (---), warm HF (---), and cold HF (· · ·). *, *P < 0.01 compared with pretreatment level. (C) VT during UF + HD (---), warm HF (---), and cold HF (· · ·). *, *P < 0.01 compared with pretreatment level.

with UF + HD when using the same temperature for dialysate and substitution fluid. In contrast to the clinical standard of 37.0°C, a dialysate temperature of 37.5°C was used to match the arterial and venous blood temperatures at the start of dialysis. To match UF + HD and HF with respect to the extracorporeal blood temperature, the infusate temperature was increased to 39.0°C in predilution HF, which resulted in an almost comparable temperature of blood in the arterial and venous line. In contrast, HF at an infusate temperature of 36.0°C was associated with cooling of blood in the extracorporeal circuit. The somewhat lower arterial blood temperature at the start of cold HF is probably the result of some degree of recirculation. The significant increase in the arterial blood temperature after 3 h UF + HD and warm HF indicates that the
net thermal balance was positive in both treatments, which is in agreement with previous studies (21, 22). Although very small, the rise in arterial blood temperature during cold HF was significant. This suggests that despite extracorporeal blood cooling, the patient's body temperature did increase, which might be related to either dialysis-induced catabolism (23) or an inadequate degree of heat loss as a result of baroreceptor-mediated vasoconstriction of the skin vasculature.

Although systemic hemodynamics were not measured in this study, changes in forearm vascular tone have been shown to correspond well with changes in splanchnic blood flow during unloading of either cardiopulmonary mechanoreceptors or arterial baroreceptors (24, 25). Moreover, improvements in vascular reactivity did result in a higher systemic BP in the study presented here. With comparable predialysis weights and changes in intravascular volume, and with UF + HD and HF matched for the buffer substrate, small molecule clearances, and biocompatibility factors, only cold HF was associated with a physiological hemodynamic response to compensate for the decrease in circulating blood volume. FVR and VT were significantly different during cold HF compared with both UF + HD and warm HF, without significant differences between the latter two treatments. These results indicate that the well-described differences in hemodynamics between UF + HD and HF are primarily related to thermal differences. The curves on FVR suggest that even UF + HD and warm HF were associated with an increase in peripheral vascular tone during the first hour. Thereafter, this increase seems to be offset most likely as result of the net positive thermal balance. In agreement, Baldamus et al. also found an increase in TPR during the first 2 h of bicarbonate dialysis, after which it tended to decrease during the following 2 h (3). (Dialysate temperature is not given.) In contrast, the cold stimulus during cold HF initiated an instantaneous increase in peripheral resistance, as well as in mean arterial pressure in this study, of which the former continued to increase during the second hour. In a previous study, using the same methods, we already found that peripheral vascular reactivity was improved during UF + HD by lowering the dialysate temperature to 35.0°C, which resulted in a significantly higher BP after 4 h of treatment compared with UF + HD performed at a dialysate temperature of 37.5°C (22).

Our study was designed primarily to investigate the phenomenon of disparity in vascular reactivity between UF + HD and HF. From a clinical point of view, it is important to notice that none of the patients experienced symptomatic hypotension during either UF + HD or warm HF. However, patients were selected on the basis of clinical hemodynamic stability during their regular dialysis treatments, together with a relatively good cardiac function. Symptomatic hypotension results from changes in both intravascular volume and vascular tone, in which the individual cardiac status defines the limits at which level changes in both parameters will lead to a decrease in arterial BP. In addition, an increase in myocardial contractility due to the influx of calcium ions could contribute to the maintenance of BP despite a decrease in blood volume and in the absence of significant increase in FVR (26). However, we cannot exclude a differentiated response of a vascular bed not studied in this study.

Our results are at variance with results obtained by Maggiore et al. (15) and Fox and Henderson (16), who concluded that differences in the extracorporeal blood temperature are only partially responsible for disparity in hemodynamic stability. However, Maggiore et al. only measured BP and heart rate, whereas acetate was used as a single buffer in UF + HD while using lactate in HF (15). The vasodilatory capacities of acetate are well described. Fox and Henderson only measured core body temperature, whereas the same temperature was used for dialysate and substitution fluid (16). Differences in arterial and venous blood temperature are not excluded in their study because core body temperature is the result of both changes in extracorporeal blood temperature and compensating mechanisms by the body.

Although plasma catecholamines only weakly reflect overall sympathetic activity (27), our data on plasma catecholamines do not confirm that improved vascular reactivity in cold HF is the result of an increase in sympathetic tone (13, 28). More direct measurements of sympathetic activity are necessary to be more conclusive on this subject (29). In addition, it is unknown whether the effects of temperature on vascular tone are more generalized or remain confined to the skin vascular bed (30, 31).

In conclusion, our study shows that the disparity in vascular reactivity between UF + HD and HF is related primarily to differences in the extracorporeal blood temperature, which indicates that it should be possible to obtain a comparable hemodynamic stability in UF + HD as in HF by lowering the dialysate temperature. Future studies are necessary to determine the optimal dialysate and infusate temperature and to investigate the possible adverse effects of cold dialysis on the incidence of cardiac arrhythmias and tissue oxygenation.

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