Effect of Ultrafiltration on Thermal Variables, Skin Temperature, Skin Blood Flow, and Energy Expenditure during Ultrapure Hemodialysis

Frank M. van der Sande,* Laura M. Rosales,† Zohar Brener,‡ Jeroen P. Kooman,* Martin Kuhlmann,‡ Garry Handelman,‡ Roger N. Greenwood,‡ Mary Carter,‡ Daniel Schneditz,§ Karel M. Leunissen,* and Nathan W. Levin†

*Division of Internal Medicine and Nephrology, University Hospital Maastricht, Maastricht, The Netherlands; †Division of Nephrology and Hypertension, Beth Israel Medical Center, Renal Research Institute, New York, New York; §Division of Nutrition, University of Massachusetts, Lowell, Massachusetts; and ‡Institute of Physiology, Medical University, Graz, Austria

The cause of the increase in core temperature (CT) during hemodialysis (HD) is still under debate. It has been suggested that peripheral vasoconstriction as a result of hypovolemia, leading to a reduced dissipation of heat from the skin, is the main cause of this increase in CT. If so, then it would be expected that extracorporeal heat flow (Jex) needed to maintain a stable CT (isothermic; T-control = 0, no change in CT) is largely different between body temperature control HD combined with ultrafiltration (UF) and body temperature control HD without UF (isovolemic). Consequently, significant differences in ΔCT would be expected between isovolemic HD and HD combined with UF at zero Jex (thermoregulation; E-control = 0, no supply or removal of thermal energy to and from the extracorporeal circulation). During the latter treatment, the CT is expected to increase. In this study, changes in thermal variables (CT and Jex), skin blood flow, energy expenditure, and cytokines (TNF-α, IL-1 receptor antagonist, and IL-6) were compared in 13 patients, each undergoing body temperature control (T-control = 0) HD without and with UF and energy-neutral (E-control = 0) HD without and with UF. CT increased equally during energy-neutral treatments, with (0.32 ± 0.16°C; P = 0.000) and without (0.27 ± 0.29°C; P = 0.006) UF. In body temperature control treatments, the relationship between Jex and UF tended to be significant (r = −0.51; P = 0.07); however, there was no significant difference in cooling requirements regardless of whether treatments were done without (−17.9 ± 9.3 W) or with UF (−17.8 ± 13.27 W). Changes in energy expenditure did not differ among the four treatment modes. There were no significant differences in pre- and postdialysis levels of cytokines within or between treatments. Although fluid removal has an effect on thermal variables, no single mechanism seems to be responsible for the increased heat accumulation during HD.


Received August 10, 2004. Accepted March 16, 2005.

Address correspondence to: Dr. Frank M. van der Sande, Department of Internal Medicine and Nephrology, University Hospital Maastricht, P. Debyelaan 25, P.O. Box 5800, Maastricht, Limburg 6202AZ, The Netherlands. Phone: +31-43-3875007; Fax: +31-43-3875006; E-mail: fvs@groupwise.azm.nl

Copyright © 2005 by the American Society of Nephrology

ISSN: 1046-6673/1606-1824
in peripheral vascular tone are solely responsible for the impressive heat accumulation observed during HD.

The thermal response to a decline in blood volume (BV) is best studied by comparing both changes in thermal variables and skin blood flow (SBF) between isovolemic HD, during which vasoreactivity is expected to be low if not abolished because UF is zero, and UF combined with HD. Comparing extracorporeal energy flow between isovolemic HD and UF combined with HD will enable the quantification of the heat stress of HD, which can be attributed to the vasoconstriction during a decline in BV. Studying heat accumulation during HD is best performed under body temperature control conditions, as changes in CT themselves may influence metabolic rate (28). Moreover, comparing the metabolic rate between isovolemic HD and UF combined with HD will lead to a further understanding of the mechanism by which a decline in BV leads to an increase in heat stress.

The hypothesis of our study was that a reduction in heat loss by a reduction in SBF, as a result of peripheral vasoconstriction in response to a decline in BV, is the main cause of heat stress during HD combined with UF. Thus, the expectation was that significant differences in extracorporeal energy flow would be observed between body temperature control treatments with and without UF and that significant differences would be observed in the change of CT between energy-neutral treatments with and without UF. The aim of this study therefore was to compare the hemodynamic response and thermal factors between isovolemic HD and HD combined with UF under body temperature control (T-control = 0, no change in CT) and energy-neutral (E-control = 0, no supply or removal of thermal energy to and from the extracorporeal circulation) conditions.

Materials and Methods

Patients and Dialysis

Thirteen stable patients who were on chronic intermittent HD were studied. Exclusion criteria were frequent hypotensive episodes during HD, a central venous catheter as access for HD, and severe coronary heart disease or heart failure (New York Heart Association class 2 or more).

Patients gave informed consent to participate in this study, approved by the Beth Israel Medical Center Institutional Review Board (New York, NY). High-efficiency HD was delivered by volumetric machines (A2008H; Fresenius Medical Care, Walnut Creek, CA) and polysulfone dialyzers (F8 and F80; Fresenius Medical Care) using ultrapure bicarbonate dialysate (Diasafe; Fresenius Medical Care). Blood flow was 400 ml/min, and dialysate flow was 800 ml/min. Endotoxin activity in dialysate was <0.96 endotoxin units/ml (limulus amoebocyte lysate test; Associates of Cape Cod, Falmouth, MA). Dialyzers were used up to 15 times and disinfected for 20 h at 95°C with 1.5% citric acid.

With each patient serving as his or her own control, measurements during this observational study were performed under T-control conditions, i.e., patient temperature was controlled to remain constant (T-control = 0), under extracorporeal E-control conditions, i.e., there was no supply or removal of thermal energy to and from the extracorporeal circulation (E-control = 0), under isovolemic conditions when treatments were done without UF, and under regular UF conditions. Each patient was studied during four consecutive HD treatments, which differed in the type of treatment given; isovolemic HD under T-control conditions (T-control = 0; HD:T-control = 0), HD combined with UF under T-control conditions (T-control = 0; HD+UF:T-control = 0), isovolemic HD under E-control conditions (E-control = 0; HD:E-control = 0), and HD combined with UF under E-control conditions (E-control = 0; HD+UF:E-control = 0). Measurements were performed in randomized order. The sessions that were done under isovolemic conditions were followed by a phase that included UF so that at the end of the whole treatment, the patients would reach their target dry weight. Data were not collected during this phase.

Because the upright position may lead to heat accumulation, all measurements were done in the supine position. Furthermore, because eating and drinking affect thermogenesis, patients refrained from eating and drinking during the measurements (29). Humidity in the room was approximately 60%.

Temperature Control

Arterial (TA) and venous (TV) blood line temperatures as well as energy transfer between the extracorporeal circuit and the patient were monitored noninvasively at 15-s intervals using air-filled measuring heads with platinum temperature sensors (BTM; Fresenius Medical Care, Bad Homburg, Germany) fitted around the arterial and venous blood lines. Energy transfer was calculated by the formula \( c \times \rho \times Q_b \times (T_{TV} - T_{TA}) \times t \), where \( c \) is specific thermal capacity (3.64 kJ/kg°C), \( \rho \) is the extracorporeal blood flow, \( Q_b \) is the density of blood (1052 kg/m^3), and \( t \) is the dialysis time in hours (30).

Energy flow rate was set during HD:E-control = 0 and HD+UF:E-control = 0 at 0 kJ/h, which means that no energy is fed to or withdrawn from the patient via the extracorporeal circuit. The automatic thermal energy balance control (E-mode) runs as follows: After the control function has been started, the BTM determines the TV required to reach the thermal energy flow rate prescribed by the user. Then the dialysate temperature (TD) is changed in such a way that the desired TV is reached. In regular intervals, the BTM examines whether there is a deviation of the actual mean energy flow rate from the setting value. If this is the case, then the TD is adjusted to compensate for the deviation within a short period of time.

In the temperature-control mode (T-mode) provided by the BTM, arterial temperatures are monitored and dialysate temperatures are adjusted by a negative-feedback loop. During HD:T-control = 0 and HD+UF:T-control = 0, the hourly change in patient temperature was set in the BTM at T-control = 0.

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 correction is necessary because arterial blood temperature is determined by the CT as well as by the temperature of any recirculating venous blood. In the BTM, recirculation is measured by a temperature bolus produced by a transient change in TA. Both the venous and the arterial line sensors of the BTM record the resulting change in blood temperatures. From the ratio in bolus amplitudes, recirculation can be calculated. Predialytic CT was defined as the first reliable temperature obtained (in all patients within 5 min) after the start of HD. The accuracy of the BTM temperature measurement is better than 0.05°C, and the reproducibility is better than 0.01°C as given by the manufacturer. It is also possible to read the instantaneous TD on the display of the BTM.

Blood Volume

Changes in BV were monitored continuously and noninvasively with the Fresenius BV monitor (BVM; Fresenius Medical Care), which measures changes in relative BV by measuring total protein concentration by ultrasonic means.
Skin Temperature

Skin temperature was measured by a Hewlett Packard device (HP 7820A; Boeblingen, Germany) with a monitoring range of 15 to 45°C, a resolution of 0.1°C, and an accuracy of 0.2°C (0.1°C instrument, 0.1°C temperature probe). Two attachable surface temperature probes (HP 21009A) were placed on the skin but not on a blood vessel of the contralateral arm of the vascular access. Measurements were done before and at the end of dialysis.

Skin Microcirculation

Skin microcirculation was studied by means of a Laser-Doppler device (Perimed KB0; Stockholm, Sweden) that measures noninvasively an integral of cutaneous blood flux in microvessels and shunts in the skin (31,32). The magnitude of cutaneous perfusion is given in arbitrary units (AU). The Laser-Doppler device was positioned at two places at the palmar side of the arm on the skin but not on a vessel. Measurements were done for 5 min before and at the end of dialysis. The arm was placed in supine position and did not move for the time of the measurement.

Energy Expenditure

Energy expenditure was obtained by indirect calorimetry (EEvmax). Concentrations of O2 and CO2 were measured continuously in exhaled air using a canopy covering the head of the patient and applying the mixing chamber technique procedure provided by a metabolic cart (Vmax29; SensorMedics Corp., Yorba Linda, CA) (33). Measurements were done for 5 min before and at the end of dialysis. The arm was placed in supine position and did not move for the time of the measurement.

Power Analysis

A power analysis using the data of van der Sande et al. (20) was performed with the 0-hypothesis—no change in CT during isovolemic energy-neutral HD (HD:E-control = 0)—and the alternative hypothesis—change in CT between the two energy-neutral sessions. The change in CT between the two energy-neutral sessions was NS. There were no significant differences between the two energy-neutral sessions. CT remained stable during T-control sessions (Figure 1). Change in CT was 0.27 ± 0.29°C during HD:E-control = 0 (NS) and 0.32 ± 0.16°C during HD+UF:E-control = 0 (NS).

CT increased significantly during energy-neutral sessions (Figure 1). Change in CT was 0.27 ± 0.29°C during HD:E-control = 0 (P = 0.006) and 0.32 ± 0.16°C during HD+UF:E-control = 0 (P = 0.000). The change in CT between the two energy-neutral sessions was NS. There were no significant differences between the time of shift (early morning or afternoon) and the change in CT.

Table 1. Baseline variables

<table>
<thead>
<tr>
<th></th>
<th>HD:T-Control = 0</th>
<th>HD+UF:T-Control = 0</th>
<th>HD:E-Control = 0</th>
<th>HD+UF:E-Control = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialysis weight (kg)</td>
<td>67.7 (12.7)</td>
<td>68.2 (12.6)</td>
<td>68.3 (12.7)</td>
<td>68.1 (12.9)</td>
</tr>
<tr>
<td>UF volume (ml)</td>
<td>3100 (1022)</td>
<td>3100 (1022)</td>
<td>3100 (1022)</td>
<td>3100 (1022)</td>
</tr>
<tr>
<td>Room temperature (°C)</td>
<td>24.06 (1.82)</td>
<td>23.78 (1.81)</td>
<td>23.06 (1.62)</td>
<td>22.24 (1.54)</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.49 (0.41)</td>
<td>36.43 (0.34)</td>
<td>36.46 (0.32)</td>
<td>36.43 (0.24)</td>
</tr>
<tr>
<td>Skin blood flow (AU)</td>
<td>3.84 (0.88)</td>
<td>3.74 (1.07)</td>
<td>3.66 (1.30)</td>
<td>3.89 (1.31)</td>
</tr>
<tr>
<td>Skin temperature (°C)</td>
<td>32.32 (1.58)</td>
<td>32.33 (1.29)</td>
<td>31.69 (1.15)</td>
<td>31.58 (0.81)</td>
</tr>
</tbody>
</table>

HD:T-control = 0, isovolemic hemodialysis under body temperature control conditions, i.e., no change in core temperature; HD+UF:T-control = 0, hemodialysis combined with ultrafiltration under body temperature control conditions; HD:E-control = 0, isovolemic hemodialysis under energy-neutral conditions, i.e., no change in energy flow; HD+UF:E-control = 0, hemodialysis combined with ultrafiltration under energy-neutral conditions; UF, ultrafiltration; AU, arbitrary units.
significant change in thermal energy in treatment modes done with HD+UFT-control = 0 (−225 ± 113 kJ; \( P = 0.000 \)) or without UF HD-T-control = 0 (−204 ± 92 kJ; \( P = 0.000 \)). The amount in thermal energy removed was not significantly different between the two T-control sessions. Moreover, there were no significant differences between the time of shift (early morning or afternoon) and the amount of thermal energy removed.

Although in one patient there was an increase in CT of 0.3°C during HD+UFT-control = 0, the energy removal was −186 kJ, which does not seem to differ from the rest of the patients. Moreover, there was no relation between changes in CT and accumulated energy removal during HD+UFT-control = 0 (\( r = 0.237; \) NS).

UF volume was found to be significantly related to the extracorporeal energy flow rate required to maintain a stable CT during HD+UFT-control = 0 (Figure 3). There was no relationship between change in BV and extracorporeal energy flow rate in any one of the four sessions.

Room temperature increased slightly but significantly during all four treatments (Table 2). However, there were no significant differences in the changes of room temperature among the four treatments. No relations between changes in room temperature and other thermal variables were observed.

In a multiple regression analysis model that included as independent variables changes in cytokine levels, changes in ST, changes in blood flow, and UF rate, with, respectively ΔCT (change in CT) and \( J_{\text{ex}} \) (energy flow rate) as dependent parameters, no significance was observed in any one of the four treatments.

**BV**

As expected, the changes in BV were almost zero during the sessions without UF, during HD=T-control = 0 the change in BV was 2.3% (3.5%), and during HD=E-control = 0 was 2.8% (1.8%). The change in BV during HD+UFT-control = 0 was −16.1% (6.7%) and during HD+UFE-control = 0 was −11.3% (6.5%).

**ST**

ST remained stable during both isovolemic sessions (Table 3) both under energy-neutral and T-control conditions. ΔST was −0.09 ± 0.87°C during HD=T-control = 0 (NS) and 0.41 ± 0.95°C during HD=E-control = 0 (NS). The difference in ΔST between the two isovolemic sessions was NS.

During both UF sessions, ST changed significantly both during T-control and energy-neutral conditions. However, the de-
Table 2. Thermal variables

<table>
<thead>
<tr>
<th></th>
<th>HD:T-Control = 0</th>
<th>HD+UF:T-Control = 0</th>
<th>HD:E-Control = 0</th>
<th>HD+UF:E-Control = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔRT (°C)</td>
<td>0.50 (0.79)b</td>
<td>0.69 (1.14)b</td>
<td>0.43 (1.10)b</td>
<td>0.63 (0.72)b</td>
</tr>
<tr>
<td>ΔCT (°C)</td>
<td>0.02 (0.05)</td>
<td>0.04 (0.13)</td>
<td>0.27 (0.29)b</td>
<td>0.32 (0.16)b</td>
</tr>
<tr>
<td>ΔThermal energy (kJ)</td>
<td>−204 (92)b</td>
<td>−225 (113)b</td>
<td>−7 (7)</td>
<td>−5 (1)</td>
</tr>
<tr>
<td>Jex (W)</td>
<td>−17.89 (9.28)b</td>
<td>−17.79 (13.27)b</td>
<td>−0.28 (2.85)</td>
<td>−0.31 (3.23)</td>
</tr>
</tbody>
</table>

*aART, change in room temperature versus baseline; ΔCT, change in core temperature versus baseline; ΔThermal energy, energy removal; Jex, thermal energy flow rate.
*bChange versus baseline, P < 0.05.

Table 3. Skin temperature and skin blood flow

<table>
<thead>
<tr>
<th></th>
<th>HD:T-Control = 0</th>
<th>HD+UF:T-Control = 0</th>
<th>HD:E-Control = 0</th>
<th>HD+UF:E-Control = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔST (°C)</td>
<td>−0.09 (0.87)b</td>
<td>−0.87 (0.91)c,d</td>
<td>0.41 (0.94)</td>
<td>0.50 (0.71)c</td>
</tr>
<tr>
<td>ΔSBF (AU)</td>
<td>0.05 (0.31)b</td>
<td>−0.93 (0.59)c,d</td>
<td>0.56 (1.29)</td>
<td>−0.46 (0.87)</td>
</tr>
</tbody>
</table>

*aΔST, change in skin temperature versus baseline; ΔSBF, change in skin blood flow; AU, arbitrary units.
*bHD:T-control = 0 versus HD+UF:T-control = 0, P = 0.012.
*cChange versus baseline, P < 0.05.
*dHD+UF:T-control = 0 versus HD+UF:E-control = 0, P = 0.012.

Increase in ST was significantly (P = 0.005) larger during the T-control compared with the energy-neutral treatment (Table 3). ΔST was −0.88 ± 0.91°C during HD+UF:T-control = 0 (P = 0.005) and 0.50 ± 0.71°C during HD+UF:E-control = 0 (P = 0.026).

SBF

SBF remained stable during both T-control and energy-neutral isovolemic sessions (Table 3, Figure 4). The change in SBF (ΔSBF) was 0.05 ± 0.31 AU during HD:T-control = 0 (NS) and 0.56 ± 1.29 AU during HD:E-control = 0 (NS). The difference in ΔSBF between the two isovolemic sessions was NS. The change in SBF during HD+UF:T-control = 0 was significant (−0.93 ± 0.59 AU; P = 0.000) but not during HD+UF:E-control = 0 (−0.46 ± 0.87 AU; P = 0.082). The difference in ΔSBF between T-control and energy-neutral treatments with UF was significant (P = 0.001). The change in SBF between HD+UF:T-control = 0 and HD:T-control = 0 was significant (P = 0.001), as was the difference in ΔSBF between HD+UF:E-control = 0 and HD:E-control = 0 (P = 0.011). In any one of the treatments, patients did not need to increase their SBF because of the increase, although small, in room temperature. There was also no relation in any one of the four treatments between SBF as a dependent variable and ST and CT as independent variables. With Pearson analysis, there was a significant positive relation (r = 0.587, P = 0.035) between change in BV and change in SBF during HD+UF:E-control = 0. There was no relation between change in BV and change in SBF during HD+UF:T-control = 0.

Energy Expenditure

EEVmax remained stable during both T-control sessions (Table 4). The change in EEVmax (ΔEEVmax) was −4.01 ± 7.62 W during HD:T-control = 0 (NS) and −0.42 ± 5.17 W during HD+UF:T-control = 0 (NS). The difference in ΔEEVmax between the two T-control sessions was NS. EEVmax remained stable during HD:E-control = 0 (−0.34 ± 7.41 W; NS) and decreased significantly during HD+UF:E-control = 0 (−2.97 ± 4.49 W; P = 0.034). The difference in ΔEEVmax between both energy-neutral sessions was NS, as was any combination between T-control and energy-neutral sessions. There were no significant differences between the time of shift (early morning or afternoon) and the change in EEVmax in any one of the sessions.

When EEVmax was calculated per body surface area, the same results as for EEVmax were observed (Table 4). Respiratory quotient showed no change at all (Table 4).
Table 4. Energy expenditurea

<table>
<thead>
<tr>
<th></th>
<th>HD:T-Control = 0</th>
<th>HD+UF:T-Control = 0</th>
<th>HD:E-Control = 0</th>
<th>HD+UF:E-Control = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔEEvmax (W)</td>
<td>–4.01 (7.62)</td>
<td>–0.42 (5.17)</td>
<td>–0.34 (7.41)</td>
<td>–2.97 (4.49)b</td>
</tr>
<tr>
<td>ΔEEvmax/BSA (W/m²)</td>
<td>–2.29 (4.58)</td>
<td>–0.34 (2.94)</td>
<td>–0.19 (4.03)</td>
<td>–1.71 (2.74)</td>
</tr>
<tr>
<td>ΔRq</td>
<td>0.00 (0.08)</td>
<td>0.00 (0.06)</td>
<td>0.00 (0.10)</td>
<td>0.00 (0.08)</td>
</tr>
</tbody>
</table>

aΔEEvmax, change in energy expenditure; ΔEEvmax/BSA, change in energy expenditure per body surface area; ΔRq, change in respiratory quotient.

Cytokines

There were no significant changes in TNF-α, IL-1-ra, and IL-6 levels measured before and after dialysis in any one of the four sessions (Table 5). There were also no significant differences in changes in these cytokines between the sessions. Also, there was no correlation between changes in cytokines and CT and extracorporeal energy flow rate.

Discussion

The primary hypothesis of this study was that large thermal differences would be present between dialysis treatments with or without UF. In contrast to expectations, no significant difference in cooling requirements was observed when T-control (isothermic) treatments were done with or without UF (i.e., the same cooling to keep the CT constant). Furthermore, under energy-neutral (thermoneutral) conditions, there was a significant increase in CT, irrespective of whether patients received UF or not.

Previous data suggested that UF-induced vasoconstriction would result in a reduction of surface blood flow, a decrease in surface heat loss, and finally an increase in CT. As a consequence of the increase in CT, the blood flow to cutaneous vascular beds is increased at a later stage of the dialysis treatment, thus antagonizing the normal vascular response to hypovolemia (26).

Indeed, SBF decreased during HD combined with UF and remained unchanged during the isovolemic treatments. Moreover, the decline in SBF during UF was significantly larger during T-control HD (during which CT is stable) compared with energy-neutral HD (during which CT increased), which is in agreement with the antagonistic effect of BP control mechanisms and thermoregulatory mechanisms acting on the same vascular bed (34). ST also decreased during T-control treatment with UF and did not change during T-control treatment without UF. In line with the studies of Rosales et al. (27,35), a positive relationship between UF volume and energy flow rate was observed during T-control treatment. Still, the equal changes in CT between energy-neutral treatments and the absence of differences in extracorporeal energy flow rate during T-control treatments with and without UF are in contrast with the above-mentioned hypothesis and suggest that factors other than reduced heat loss by peripheral vasoconstriction are involved in heat accumulation during dialysis.

Especially changes in ST and SBF would be expected to be of importance in potential differences in thermal parameters (CT and energy flow rate) between treatments with and without UF, because of a reduced heat dissipation from the skin. In this study, it was shown that SBF and ST decreased during HD+UF:T-control = 0 in contrast to HD:T-control = 0. That despite this finding no differences in energy flow rate and accumulated energy removal were observed points to the importance of other, yet-undefined factors in the pathogenesis of thermal changes during HD.

Apart from reduced heat loss, an increased metabolic rate during dialysis might lead to heat accumulation (25). In our study, changes in EEvmax were not significantly different during the four treatment sessions, suggesting that changes in metabolic rate were neither the cause or the consequence of the increase in CT during HD under energy-neutral conditions nor the cause or the consequence of increased heat removal under T-control conditions. Our results are discrepant with those of Ikizler et al. (25). However, the results of the latter study are difficult to interpret without information on CT, dialysate temperature, and purity of water (endotoxin level) for the preparation of dialysate. A reduced heat loss from the skin might also be due to environmental factors. During the treatments, room temperature increased by approximately 0.5°C. However, it seems unlikely that a change in environmental temperature will lead to a change in CT of the same magnitude. Moreover, changes in room temperature were equal among the four different treatments and were not related to any other thermal changes.

Table 5. Cytokinesa

<table>
<thead>
<tr>
<th></th>
<th>HD:T-Control = 0</th>
<th>HD+UF:T-Control = 0</th>
<th>HD:E-Control = 0</th>
<th>HD+UF:E-Control = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔIL-1-ra (pg/ml)</td>
<td>–10.8 (30.7)</td>
<td>–143.9 (183.5)</td>
<td>11.8 (87.8)</td>
<td>23.8 (102.8)</td>
</tr>
<tr>
<td>ΔIL-6 (pg/ml)</td>
<td>0.6 (7.3)</td>
<td>4.4 (12.8)</td>
<td>15.5 (10.3)</td>
<td>5.7 (12.1)</td>
</tr>
<tr>
<td>ΔTNF-α (pg/ml)</td>
<td>1.5 (3.5)</td>
<td>7.7 (28.2)</td>
<td>–2.9 (7.0)</td>
<td>–0.8 (7.5)</td>
</tr>
</tbody>
</table>

aΔIL-1-ra, change in IL-1 receptor antagonist; ΔIL-6, change in IL-6; ΔTNF-α, change in TNF-α.
variables. Since the publication of the “IL hypothesis,” the
effects of uremia and HD on the production of especially IL-1, 
TNF, and IL-6 by peripheral mononuclear cells have been stud-
ied extensively (36). An increase in cytokine generation might
increase CT by stimulation of the anterior hypothalamic area 
(37). However, in this study, pre- and postdialysis values of
TNF-α, IL-1-α, and IL-6 did not change during the different
sessions and were not related to thermal variables.

From a theoretical point of view, backfiltration of contami-
nated dialysate could play a causative role in the pathogenesis
of thermal changes during HD. In this study, 180 and 18 di-
alyzers were used. However, as also shown by the negative
microbiological cultures of the dialysate and limbus amoeb-
cyte lysate tests, ultrapure dialysate (achieved by filtration of
the dialysate through a Diasafe membrane [Fresenius Medical
Care]) was used. Thus, it seems unlikely that backfiltration
played a role in the thermal changes observed in this study.

Thus, although fluid removal has an effect on thermal vari-
ables, we could not confirm that hypovolemia by a reduction
in SBF is the single cause of the increase in CT during HD.
Moreover, metabolic rate and changes in cytokine levels did not
seem to be responsible. Other factors, such as a removal of
factors that decrease CT such as adrenomedullin during dialy-
sis, or a circadian rhythm of CT deserve consideration (38).
Nevertheless, although the number of patients included in the
study is too small for definite conclusions, no difference in
thermal variables was observed between patients who were
studied during morning and afternoon sessions. Moreover,
metabolic rate, which is believed to be a driving force for
circadian changes in CT (39), did not change during the study.

In conclusion, although fluid removal has an effect on ther-
mal variables, no single mechanism seems to be responsible for
the increased heat accumulation during HD.

References

1. Ritz E, Rambasek M, Mall G, Ruffman K, Mandelbaum A: 
Cardiac changes to uremia and their possible relation to
cardiovascular instability on dialysis. Contrib Nephrol 78:
221–229, 1990

2. Henderson LW: Hemodynamic instability during hemodi-

3. Heber ME, Lahari A, Thompson D, Raftery EB: Barorecep-
tor, not left ventricular dysfunction, is the cause of hemody-

4. Palmer F, Henrich WL: The effect of dialysis on left ven-
tricular contractility. In: Cardiac Dysfunction in Chronic Ure-
mia, edited by Parfrey PS, Harnett JD, Dordrecht, Kluwer
Academic, 1992, pp 171–186

5. Yellin EL, Nikolic S, Frater RWM: Left ventricular filling

compliance in end-stage renal failure. Kidney Int 37: 137–
142, 1990

Hooff JP, Leunissen KML: Role of the venous system in
hemodynamics during ultrafiltration and bicarbonate dial-

8. Maggiore Q, Pizzarelli F, Sisca S, Zocalli C, Parlongo S,
Nicolò F, Creazzo G: Blood temperature monitor and vas-
cular stability during haemodialysis and hemofiltration. 

9. Maggiore Q, Pizzarelli F, Zocalli C, Sisca S, Nicolò F: 
Influence of blood temperature on vascular stability during 
haemodialysis and isolated ultrafiltration. Int J Artif Organs
8: 175–178, 1985

Righetto F, Scarfoterla F, Onesti G, Bazzato G: Cold as car-
diovascular stabilizing factor in hemodialysis: Hemody-
amic evaluation. Trans Am Soc Artif Intern Organs 29:
71–75, 1983

11. Mahida BH, Dumler F, Zasuwa G, Fleig G, Levin NW: 
Effect of cooled dialysate on serum catecholamines and 
blood pressure stability. Trans Am Soc Artif Intern Organs
29: 384–388, 1983

12. Swartz RD, Fitzgerald FT, Kalousdian S, Rudd M: Hypo-
thermia in the uremic patient. Dial Transplant 12: 584–590,
1983

Henry WL: Effects of cooler temperature dialysate on 
hemodynamic stability in “problem” dialysis patients. Kid-
ney Int 44: 606–612, 1993

14. Levy FL, Grayburn PA, Foulks C J, Brickner ME, Henrich
WL: Improved left ventricular contractility with cool tem-

15. Fox SD, Henderson LW: Cardiovascular response during 
hemodialysis and hemofiltration: Thermal, membrane, and

16. van Kuijk WH, Luik AJ, de Leeuw PW, van Hooff JP,
Nienman FH, Habets HM, Leunissen KM: Vascular reactiv-
ity during hemodialysis and isolated ultrafiltration: Ther-

17. van Kuijk WH, Hillion D, Savoio C, Leunissen KM: Critical 
role of the extracorporeal blood temperature in the hemo-
8: 949–955, 1997

18. Keijman JMG, van der Sande FM, Kooman JP, Leunissen
KML: Thermal energy balance and body temperature: 
Comparison between isolated ultrafiltration and haemodi-
alysis at different dialysate temperatures. Nephrol Dial
Transplant 14: 2196–2200, 1999

19. Fine A, Penner B: The protective effect of cool temperature
dialysate is dependent on patients’ predialysis tempera-

20. van der Sande FM, Kooman JP, Burema JJH, Hameleeers P,
Kerkhofs AM, Barendregt JM, Leunissen KM: Effect of 
dialysate temperature on energy balance during hemodi-
alysis: Quantification of extracorporeal energy transfer. 
Am J Kidney Dis 33: 1115–1121, 1999

21. Schneditz D, Martin K, Krämer M, Kenner T, Skrabal F: 
Effect of controlled extracorporeal blood cooling on ultra-
filtration-induced blood volume changes during hemodi-

22. van der Sande FM, Gladziwa U, Kooman JP, Boccker G,
Leunissen KML: Energy transfer is the single most impor-
tant factor for the difference in vascular response between
isolated ultrafiltration and hemodialysis. J Am Soc Nephrol
11: 1512–1517, 2000

23. Schneditz D, Levin NW: Keep your temper: How to avoid 
heat accumulation in haemodialysis. Nephrol Dial Trans-
plant 16: 7–9, 2001