Dialysis Therapies

The Effects of Control of Thermal Balance on Vascular Stability in Hemodialysis Patients: Results of the European Randomized Clinical Trial

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• ***Background:*** **Many reports note that the use of cool dialysate has a protective effect on blood pressure during hemodialysis (HD) treatments. However, formal clinical trials in which dialysate temperature is tailored to the body temperature of appropriately selected hypotension-prone patients are lacking.** ***Methods:*** **We investigated the effect of thermal control of dialysate on hemodynamic stability in hypotension-prone patients selected from 27 centers in nine European countries. Patients were eligible for the study if they had symptomatic hypotensive episodes in 25% or more of their HD sessions, assessed during a prospective screening phase over 1 month. The study is designed as a randomized crossover trial with two phases and two treatment arms, each phase lasting 4 weeks. We used a device allowing the regulation of thermal balance (Blood Temperature Monitor; Fresenius Medical Care, Bad Homberg, Germany), by which we compared a procedure aimed at preventing any transfer of thermal energy between dialysate and extracorporeal blood (thermoneutral dialysis) with a procedure aimed at keeping body temperature unchanged (isothermic dialysis).** ***Results:*** **One hundred sixteen HD patients were enrolled, and 95 patients completed the study. During thermoneutral dialysis (energy flow rate: $\Delta E = -0.22 \pm 0.29$ kJ/kg * h), 6 of 12 treatments (median) were complicated by hypotension, whereas during isothermic dialysis (energy flow rate: $\Delta E = -0.90 \pm 0.35$ kJ/kg * h), the median decreased to 3 of 12 treatments ($P < 0.001$). Systolic and diastolic blood pressures and heart rate were more stable during the latter procedure. Isothermic dialysis was well tolerated by patients.** ***Conclusion:*** **Results show that active control of body temperature can significantly improve intradialytic tolerance in hypotension-prone patients.**

INDEX WORDS: Hemodialysis (HD); hypotension; energy balance; blood temperature monitoring; dialysate temperature; dialysis tolerance.

Editorial, p. 426

SYMPTOMATIC hypotension is the most frequent acute complication affecting patients during chronic hemodialysis (HD) treatment sessions. Although not yet fully elucidated, the origin of hypotension is clearly multifactorial; some factors are patient related and others are dialysis-treatment technique related. Among these, dialysate temperature has been shown to have an important role. Since the first original reports in the early 1980s,[1-4] many studies have confirmed that if dialysate temperature is adjusted to the range of 34°C to 35.5°C, cardiovascular tolerance to HD treatment is better than if dialysate temperature is set to 37°C or higher.[5-15] The use of warmer dialysate is associated with an increase in core body temperature,[2,5,16] shown to interfere with the appropriate hemodynamic response to body fluid removal, thus favoring the

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For the Study Group of Thermal Balance and Vascular Stability (see Appendix).

Received November 16, 2001; accepted in revised form February 19, 2002.

Supported in part by Fresenius Medical Care AG.

Presented in part at the 32nd Annual Meeting of the American Society of Nephrology, Miami Beach, FL, November 5-8, 1999.

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0272-6386/02/4002-0008$35.00/0

doi:10.1053/ajkd.2002.34506

onset of hypotensive episodes in predisposed patients.[2,7,12,15-20] Conversely, the use of dialysate at a lower temperature, which has little effect on or even reduces body temperature, favors the appropriate cardiovascular response to fluid removal.[7,12,15,18-21] However, data are lacking about the optimal dialysate temperature that does not expose patients to the uncomfortable cold stress reported by several investigators, while affording a protective effect on cardiovascular stability.[9,12,22]

Early studies[1-4] used very low dialysate temperatures (<35°C) with the aim of reproducing as closely as possible the thermal setting of procedures alleged to provide the best protection of cardiovascular stability, such as isolated ultrafiltration and hemofiltration. Because body hyperthermia induced by dialysis treatment is an important factor predisposing to hypotension,[5,12,16-19,23] it would appear more logical to manipulate dialysis thermal setting to prevent heat accumulation in the body, rather than inflict an empirical cold stress.[24] Pursuing such a goal implies that dialysate temperature should be modulated according to the needs of the individual patient because pre-HD body temperatures vary widely among patients,[22] and increases in body temperature vary according to their ultrafiltration requirement.[25]

With the present study, we aim to investigate whether preventing the hyperthermic response has favorable effects on hemodynamic stability during the HD procedure while affording good tolerance to patients. In contrast to most previous studies in which a fixed dialysate temperature was applied,[1-15,21,22,26] we used a device allowing feedback regulation of thermal balance according to the patient's individual body temperature. The study was performed as a randomized crossover trial comparing a procedure aimed at preventing any transfer of thermal energy between dialysate and extracorporeal blood circulation with a procedure aimed at keeping body temperature unchanged. The study involved only patients with a documented predisposition to develop dialysis hypotension and had as its main objective the evaluation of the effect of thermal balance on the frequency of dialysis sessions complicated by symptomatic hypotensive episodes, identified on the basis of a set of predefined criteria.

PATIENTS AND METHODS

Study Population

Study patients were selected from 27 centers in nine European countries.

Inclusion criteria. To be eligible for the study, patients had to meet the following criteria: (1) symptomatic hypotensive episodes occurring in 25% or more of HD sessions, (2) minimum age of 18 years, (3) on HD therapy for at least 3 months, and (4) treatment with standard HD three times weekly using bicarbonate buffer and with a treatment duration of at least 180 minutes. A hypotensive episode was defined as the sudden onset of symptomatic hemodynamic changes that could be relieved by specific interventions. Hemodynamic changes were defined as follows: (1) reduction in systolic blood pressure of at least 25 mm Hg accompanied by any of the following symptoms: nausea, vomiting, muscle cramps, dizziness, or fainting; (2) a sensation of dizziness and/or fainting, even if the decrease in blood pressure was less than 25 mm Hg; or (3) sudden onset of a sensation of dizziness and/or fainting requiring immediate intervention, even if systolic blood pressure was not coincidentally recorded or was not measurable.

Specific interventions for symptomatic hypotension were defined as follows: Trendelenburg's position, administration of saline, administration of hypertonic solution, administration of plasma expander, and premature discontinuation of the dialysis session. To verify their predisposition to intradialytic hypotension, patients participated in a 4-week prospective screening phase during which the incidence of hypotensive episodes was recorded. Patients were enrolled if at least 3 of 12 consecutive HD sessions were complicated by hypotensive episodes.

Exclusion criteria. Patients were not eligible for participation for any of the following reasons: recent surgical intervention, severe anemia (hematocrit < 25%), intercurrent illnesses, problems related to vascular access, diffuse neoplastic disease, ascites, class IV heart failure according to the New York Heart Association, obligatory use of a single needle or central venous catheter with single lumens, use of antihypotensive drugs, treatment with extracorporeal blood purification techniques other than HD, or participation in another clinical study.

In accordance with national regulations in various countries, the study was submitted to local ethics committees for approval. Patients were asked to give written informed consent before being enrolled onto the trial.

Study Design

The main objective of the trial is to compare the effect of two different levels of thermal balance on the frequency of dialysis sessions complicated by symptomatic hypotension. For this purpose, we devised a randomized open trial with a crossover design allowing intrapatient comparison that involved two phases and two treatment arms. This study design was used on the assumption that the initial treatment would not exert a carryover effect on the following one. After enrollment, patients were kept on standard HD treatment during a 1-week run-in period. Subsequently, patients were randomly assigned to treatment sequence A to B or B to A, each phase lasting 4 weeks. Randomization was per-

formed centrally in blocks of four patients, and separate randomization lists were provided for each center.

Treatment Characteristics

In the control procedure, thermoneutral HD,[23] the target was to minimize heat exchange between extracorporeal blood and dialysate (energy flow rate: $\Delta E = 0$ kJ/h), such that no heat energy was transferred to or from the patient. Thus, changes in body temperature are caused by factors other than heat gain or loss through the extracorporeal blood circuit. The study procedure, isothermic HD,[25] was designed to maintain body temperature constant throughout the dialysis sessions (Δbody temperature = 0°C/h).

Apart from these differences in thermal balance, all other treatment parameters had to remain unchanged throughout the entire study: ie, prescribed dialysate composition, type of dialyzer, duration of treatment, dialysis frequency, adjustment of dialysis treatment, blood and dialysate flow, target body weight, ultrafiltration and sodium profiles (when applicable), mean interdialytic body weight increase, posture during dialysis, permission to eat during HD treatment, and erythropoietin and antihypertensive treatment.

Thermal balance was controlled by means of a Blood Temperature Monitor (BTM; Fresenius Medical Care, Bad Homberg, Germany), which was integrated into standard HD machines (2008 or 4008 series; Fresenius Medical Care). The operation of this module has been described previously.[23,27] In brief, the BTM can be used to noninvasively measure temperature in the arterial and venous catheters of extracorporeal blood circulation with an accuracy to less than 0.1°C.[27] On the basis of arterial and venous blood temperature and blood flow rate measurements, with correction for blood heat capacity, the BTM can calculate thermal energy flow to the patient. Arterial blood temperature corrected for fistula blood recirculation approximately reflects core body temperature. Recirculation was measured using the thermodilution method of the BTM.[27] Through the feedback loop connecting the arterial and venous blood temperature sensor with the dialysate thermostat in the machine,[23] the device can modulate dialysate temperature to maintain unchanged either body temperature (the target of isothermic HD) or energy flow rate across the extracorporeal circuit (the target of thermoneutral HD).

Outcome Variables

The main outcome variable was frequency of HD sessions complicated by one or more hypotensive episodes. Hypotension episodes were defined identically as described for the screening phase.

As a secondary outcome variable, we assessed the effect of the two treatments on blood pressure and heart rate throughout HD sessions.

All episodes of symptomatic hypotension occurring during HD sessions were recorded on a prepared form, together with their time of occurrence and type of intervention administered. Blood pressure and heart rate were measured by either noninvasive systemic blood pressure monitoring devices or manually. Dialysate, arterial, and venous temperatures, together with thermal energy flow rate and total thermal energy balance, were recorded automatically by the BTM. Blood pressure and heart rate were measured pre-HD, post-HD, and at 30-minute intervals during treatment. Because of the time lag required for equilibration, initial BTM recordings were made 30 minutes after the beginning of the HD session and subsequently every 30 minutes until the end of the session. Basal energy expenditure was estimated using the Harris-Benedict equation.[28]

Blood samples were obtained pre-HD, post-HD, 70 minutes from the start of the midweek session of the run-in phase, and in the last week of each treatment phase for the analysis of treatment efficacy and various control parameters. Clinical and biochemical parameters were determined by using routine laboratory methods. Calculation of Kt/V was performed using the Daugirdas second-generation formula,[29] whereas equilibrated postdialysis blood urea nitrogen level was estimated according to Smye et al.[30]

Dropouts

Criteria for withdrawal of patients from the trial were the appearance during the study of any of the clinical complications listed in exclusion criteria, changes to antihypertensive medications, need to adjust estimated dry body weight by more than 1% during a 4-week period, need to change the weekly dialysis schedule or dialysis modality, kidney transplantation, transfer to another center, problems related to vascular access impairing blood flow delivery to the dialyzer (blood flow $<$ 200 mL/min), onset of major arrhythmia requiring specific treatment, or withdrawal on patient request.

Sample Size Estimate and Statistical Analysis

Sample size estimate was based on the hypothesis that in comparison with thermoneutral HD, isothermic HD would reduce the frequency of HD sessions complicated by symptomatic hypotension by 50%. To detect a reduction in frequency of sessions with hypotension from 30% to 15% with a power of 0.8 and at a significance level of P less than 0.05, a sample of 95 patients is required. The estimated sample size to allow for a 10% dropout rate thus would be 105 patients.

Statistical analysis of efficacy was conducted using Wilcoxon's nonparametric test to rank differences in number of sessions with hypotension during the two treatments in each patient (SPSS statistical software package, version 10.0; SSPS Inc, Chicago, IL). Variance was analyzed by means of paired t-test or analysis of variance, when appropriate. Unless otherwise specified, results are expressed as mean $\pm$ SEM or median and 25th to 75th quartiles. For P less than 0.05, statistical significance is assumed.

RESULTS

Patient Characteristics

One hundred sixteen hypotension-prone patients were enrolled onto the study and randomly assigned to the two treatment sequences. During the screening phase of the study, a median of 6.5 of 12 consecutive dialysis sessions were complicated by symptomatic hypotension (Fig 1).

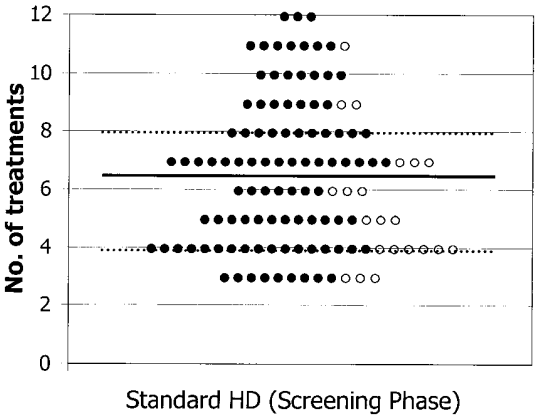

Fig 1. Frequency of HD treatments with symptomatic hypotension during the screening phase. (●), Patients completing the study; (○), dropouts. The thick horizontal line represents the median; dotted lines, 25th and 75th percentiles in the entire population.

Ninety-five patients completed the study, whereas 21 patients dropped out. The median number of complicated treatments in those who completed the study was six. Withdrawal was caused by adjustment of dry body weight by more than 1% (n = 4), surgical intervention (n = 2), vascular access problems (n = 1), change in antihypertensive treatment (n = 1), kidney transplantation (n = 1), technical problems (n = 4), at the request of the patient (n = 7), and other reasons (n = 1). Patient flow in the trial is shown in Fig 2.

As listed in Table 1, main baseline characteristics of patients who dropped out of the study did not differ substantially from those of patients who completed the study. Enrolled patients were predominantly old, women, and had a high prevalence of comorbid conditions. Twenty-five patients underwent treatment using cellulose membranes; 28 patients, modified cellulose membranes; and 63 patients, synthetic membranes of either low-flux or high-flux type. Fourteen patients were treated with ultrafiltration profiles, and 18 patients, with sodium profiles. The average percentage of interdialytic body weight increase was 3.98% ± 1.33%. Twenty-seven patients were administered antihypertensive medication. Patients underwent bicarbonate HD therapy three times weekly for a mean treatment duration of 235 ± 23 minutes.

Thermal Balance During Treatment

During thermoneutral HD, both arterial and venous temperatures increased by 0.47° C in the period from 30 to 210 minutes (Table 2; Fig 3A), whereas dialysate temperatures increased by 0.48°C (Table 2) to 37.5°C (Fig 4). Because venous temperature was slightly lower than arterial temperature (Fig 3A), the energy flow rate was slightly negative (Table 2). During isother-

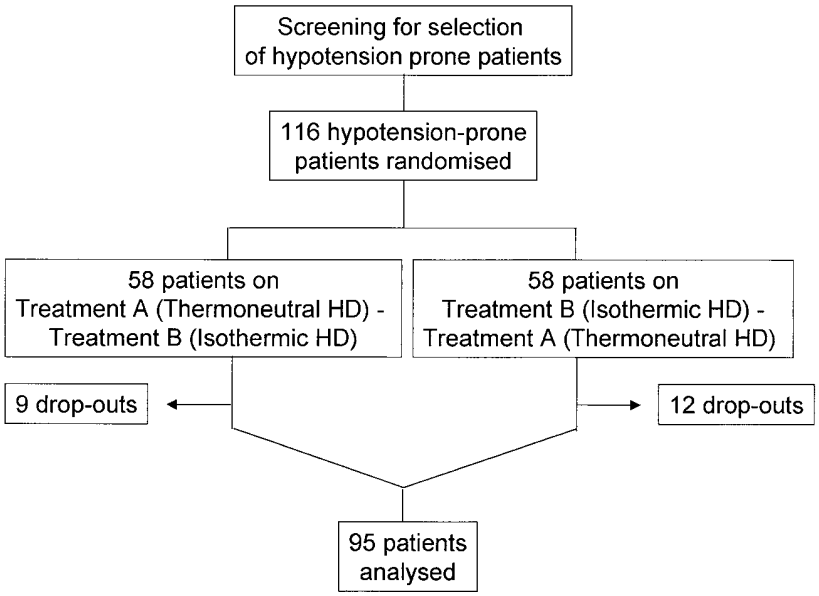

Fig 2. Trial profile.

Table 1. Patient Characteristics at Baseline

	Study Completers (N = 95)	Dropouts (N = 21)
Demography		
Age (y)	66 ± 12	69 ± 9
Sex (women/men)	58 (61)/37 (39)	12 (57)/9 (43)
Primary renal disease		
Primary glomerulonephropathy	17 (18)	5 (24)
Pyelonephritis	13 (14)	0 (0)
Interstitial nephritis	11 (12)	2 (10)
Vascular diseases	15 (16)	2 (10)
Secondary glomerular/systemic diseases	11 (12)	3 (14)
Others/unknown	28 (29)	9 (43)
Comorbidities		
Diabetes	23 (24)	2 (10)
Coronary artery disease	24 (25)	4 (19)
Arrhythmia	11 (12)	2 (10)
Previous myocardial infarction	11 (12)	1 (5)
Heart failure		
Class I	7 (7)	2 (10)
Class II	10 (11)	3 (14)
Class III	6 (6)	0 (0)
Peripheral arteriopathy	17 (18)	2 (10)
Sessions with symptomatic hypotension in screening phase (%)	50 (6, 4-8)	50 (6, 4-7)

NOTE. Values expressed as mean ± SD; number (percent), or median (25th, 75th quartile).

mic HD, arterial temperatures remained almost unchanged, whereas venous temperatures decreased by 0.9°C (Table 2; Fig 3B), reflecting the decrease in dialysate temperature by 1.11°C (Table 2) to 35.7°C (Fig 4). As a result, total thermal energy balance was only slightly negative during thermoneutral HD (−50.7 ± 61 kJ), whereas it was markedly negative during isothermic HD, with a loss of 219.3 ± 77 kJ ($P <$ 0.001; Table 2). This loss corresponds to 24% of basal energy expenditure during the approximately 4 hours of HD treatment (903 ± 129 kJ). It is of interest that to achieve the specified treatment goals, it was necessary to gradually vary the dialysate temperature during both treatments so that eventually (after 210 minutes) there was a difference of 1.76°C between the two procedures (Fig 4).

Table 2. Thermal Balance and Changes in Blood and Dialysate Temperature During the Two Treatment Types

	Thermoneutral HD	Isothermic HD	*P*
Thermal energy flow rate (kJ/kg * h)	−0.22 ± 0.29	−0.90 ± 0.35	<0.001
Thermal energy balance (kJ/treatment)	−50.7 ± 61	−219.3 ± 77	<0.001
T_{dial} at 30 min (°C)	37.07 ± 0.41	36.78 ± 0.43	<0.001
ΔT_{dial}, 210-30 min (°C)	+0.48 ± 1.13	−1.11 ± 0.48	<0.001
T_{art} at 30 min (°C)	36.58 ± 0.27	36.58 ± 0.30	NS
ΔT_{art}, 210-30 min (°C)	+0.47 ± 0.24	+0.01 ± 0.16	<0.001
T_{ven} at 30 min (°C)	36.40 ± 0.39	36.26 ± 0.39	<0.001
ΔT_{ven}, 210-30 min (°C)	+0.47 ± 0.39	−0.90 ± 0.4	<0.001

NOTE. Values expressed as mean ± SD.
Abbreviations: T_{dial}, dialysate temperature; T_{art}, arterial temperature; T_{ven}, venous temperature; NS, not significant.
*3.6 kJ/h = 1 W.

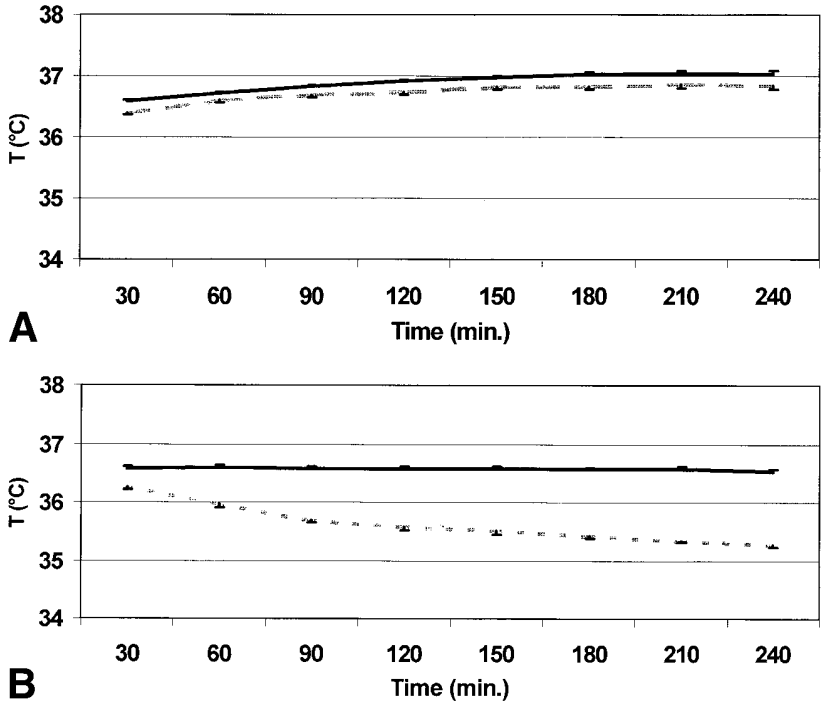

Fig 3. Changes in (—) arterial (Tart) and (- - -) venous fistula temperature (Tven) during (A) thermoneutral HD and (B) isothermic HD. Values expressed as mean ± SEM.

Hemodynamic Effects of Differences in Thermal Balance

During thermoneutral HD, the median frequency of sessions complicated by hypotension was 6 of 12 (Fig 5), ie, nearly identical to that recorded during the screening phase of the study, although 16 patients (17%) had a frequency of symptomatic treatments less than 3 of 12 sessions, ie, less than the threshold stipulated for admission onto the study.

During isothermic HD, the proportion of dialysis sessions complicated by hypotension decreased to 3 of 12 sessions ($P < 0.001$ versus thermoneutral HD; Fig 5). Overall, 66 of 95 patients (70%) responded to isothermic HD with a lower frequency of hypotensive sessions.

There were no differences in mean predialysis blood pressures and heart rates between crossover periods (systolic blood pressure, 131 ± 25 versus 130 ± 30 mm Hg; diastolic blood pressure, 70 ± 14 versus 70 ± 12 mm Hg; heart rate, 75 ± 10 versus 76 ± 9 beats/

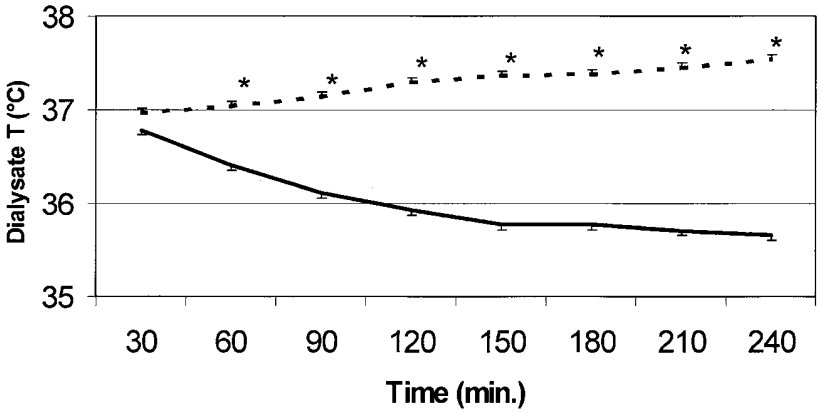

Fig 4. Dialysate temperatures during (- - -) thermoneutral HD and (—) isothermic HD. Values given as mean ± SEM. *$P < 0.05$.

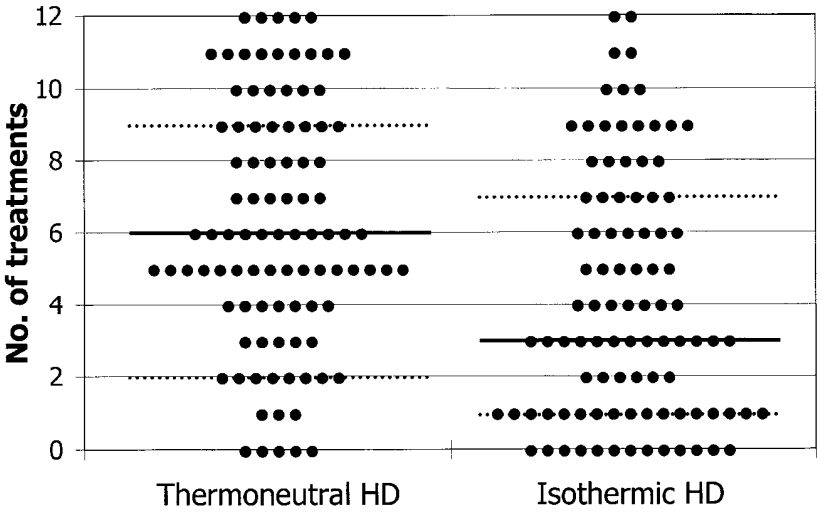

Fig 5. Frequency of HD treatments with symptomatic hypotension for each 4-week phase of the two treatments; each dot represents a patient; thick horizontal lines, the median; dotted lines, 25th and 75th percentiles. *P* < 0.001, Wilcoxon's signed rank test.

min; thermoneutral HD versus isothermic HD, respectively). During HD sessions, blood pressure decreased during both treatment modes, but to a lesser extent in isothermic HD than thermoneutral HD (Fig 6A; Table 3). Differences became statistically significant after 90 minutes ($P < 0.05$). The increase in heart rate also was less pronounced during isothermic HD; differences also became statistically significant ($P < 0.05$) after 90 minutes (Fig 6B). In addition to these hemodynamic effects, isothermic HD also caused a significant decrease in mean number of hypotensive episodes per dialysis session, from 0.83 to 0.51 ($P < 0.01$).

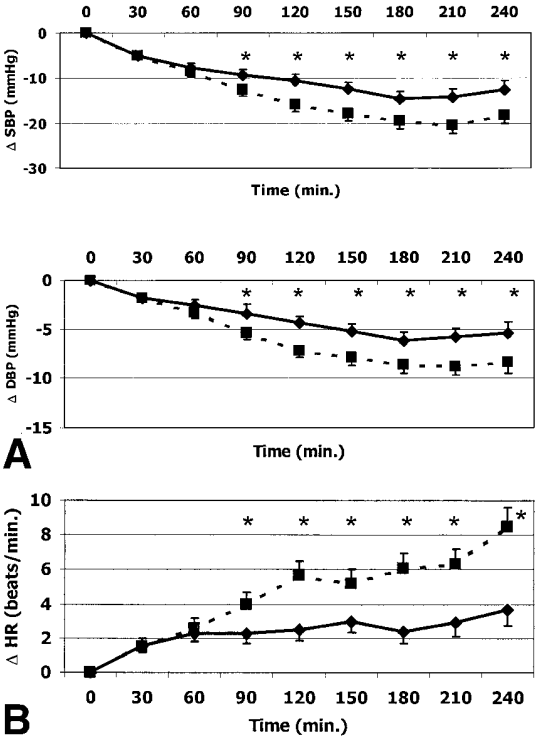

Fig 6. Changes over time in (A) systolic (ΔSBP) and diastolic blood pressure (ΔDBP) and (B) heart rate (ΔHR) during the two treatments. Values given as mean ± SEM. *$P < 0.05$. (- ■ -) Thermoneutral HD; (-◆-) isothermic HD.

Effects on Other Variables

There were no significant changes in hematocrit or total protein values during the two study phases. Pre-HD and post-HD body weights, as well as relative changes in body weight during the treatment, were not different between the two study phases (pre-HD body weight, 67.2 ± 13.1

Table 3. Changes in Hemodynamic Parameters During the Two Treatment Types

	Thermoneutral HD	Isothermic HD	*P*
ΔSystolic blood pressure, 210-0 min (mm Hg)	−20.5 ± 15.7	−14.2 ± 16.5	<0.05
ΔDiastolic blood pressure, 210-0 min (mm Hg)	−8.8 ± 8.4	−5.8 ± 8.1	<0.05
ΔHeart rate, 210-0 min (beats/min)	6.3 ± 8.1	2.9 ± 7.1	<0.05

NOTE. Values expressed as mean ± SD.

and 67.1 ± 13.1 kg; post-HD body weight, 64.8 ± 12.9 and 64.7 ± 12.9 kg; change in body weight, 3.7% ± 1.1% and 3.7% ± 1.1% for thermoneutral HD and isothermic HD, respectively). The use of cooler dialysate did not decrease dialysis efficiency, assessed by equilibrated Kt/V and urea reduction rate (Table 4).

Treatment Safety

Patients did not experience major side effects during the study phases. There was no statistically significant difference between treatment settings regarding number of sessions during which arrhythmia occurred. Patients more often reported feeling warm during thermoneutral HD (in 2 of 12 sessions, on average) than feeling cool during isothermic HD (0.6 of 12 sessions). No shivering was reported by patients. None of the patients who dropped out of the study declared that exposure to cool dialysate was the reason for their decision to withdraw.

DISCUSSION

On this study, we found that regulation of thermal balance to maintain pre-HD body temperature (isothermic HD) had a more favorable effect on the cardiovascular stability of hypotension-prone patients than a technique that aims to prevent changes in thermal balance within the extracorporeal circuit (thermoneutral HD). Compared with thermoneutral HD, isothermic HD halved the frequency of sessions complicated by symptomatic hypotensive episodes without significantly impairing treatment efficiency, and all other dialysis variables remained unchanged. Although significant from minute 90 onward, differences in blood pressure and heart rate during the course of HD sessions were less impressive than the difference in incidence of hypotensive episodes. However, use of blood pressure values alone seems inappropriate for the evaluation of the cardiovascular benefit of such techniques because any intervention at each hypotensive episode can markedly influence the course of blood pressure values over time. Because patients required a substantially greater number of interventions per session during thermoneutral HD than isothermic HD, it is probable that we have underestimated the true difference in blood pressure values between the two treatments. Overall, results show that with all other dialysis variables unchanged, observed hemodynamic changes are to be interpreted as effects of thermal manipulations.

Table 4. Comparison of Other Variables Between the Two Treatment Types

	Thermoneutral HD	Isothermic HD	*P*
Kt/V_{eq}	1.40 ± 0.47	1.37 ± 0.36	NS
Urea reduction rate (%)	73.0 ± 8.1	73.9 ± 6.6	NS
Hematocrit (%)	32.9 ± 4.2	32.9 ± 4.1	NS
Total protein (g/dL)	6.83 ± 0.5	6.84 ± 0.6	NS
Postdialytic body weight (kg)	64.7 ± 12.9	64.6 ± 12.9	NS

NOTE. Values expressed as mean ± SD.

Abbreviations: NS, not significant; Kt/V_{eq}, equilibrated Kt/V.

This study recruited a population with a predisposition to recurrent hypotensive episodes that was strictly defined and verified in a prospective screening phase. Moreover, the two treatments, each lasting 4 weeks, were assigned randomly to two reversed sequences, thus providing a safeguard against the time effect, ie, natural changes in the incidence of hypotension that occur over time. The importance of this safeguard is shown by the observation that 16 of 95 patients did not reach the threshold hypotensive response (at least 3 of 12 treatments disturbed by hypotensive episodes) during thermoneutral HD.

One important drawback of cool dialysis is its poor tolerance.[9,12,22] Instead of the fixed low dialysate temperature used in most previous studies, we used a feedback system allowing the removal of extra heat accumulated in the body during the HD treatment. This system produced changes in dialysate temperature that were more gradual than those in previous studies, shown by reaching the nadir temperature during isothermic HD toward the end of the session, when hypotensive episodes are most likely to occur. The cooling also was slight only: nadir dialysate temperature was 35.7°C, which is greater than the range of values previously reported from most studies.[1-17] That clinically relevant effects were observed even with such minor cooling of the dialysate increases the safety of the procedure and may help explain its good tolerance by patients, none of whom reported shivering during isothermic HD.

Was better tolerance gained at the expense of decreased efficacy of the milder cooling? Lacking direct comparisons, we can rely only on literature data. The 50% reduction in frequency of complicated dialysis sessions obtained using isothermic HD on this study compares well with that reported by Orofino et al,[14] who observed a 45% reduction in incidence of symptomatic hypotension in a much smaller population of high-risk patients in whom a fixed dialysate temperature of 35°C was used. Comparison with other studies is less helpful because either their study design does not allow us to establish the frequency of treatments complicated by hypotensive episodes or their patient population had a substantially lower risk than ours.[22] Thus, available data do not suggest that better tolerance was gained at the expense of efficacy.

It might be argued that the favorable response to isothermic HD could be ascribed to the comparison made with thermoneutral HD requiring a relatively high dialysate temperature (37.5°C), which could have promoted a greater incidence of symptomatic hypotensive episodes than that observed in routine practice. However, this temperature was reached only toward the end of the session; average dialysate temperature during the entire session was 37.3°C. Considering the accuracy in temperature regulation by dialysis machines, ie, $\pm 0.5°$ C (stated by manufacturers' information sheets about the performance of the newer dialysis machines) and the range in dialysate temperature settings reported under the designation of standard HD (ie, from 36.9° C to 37.5°C[8,24,26]),we surmise that values recorded during our thermoneutral HD sessions were substantially within the range actually implemented during standard HD in everyday practice.

Our control procedure did not substantially alter the hemodynamic response observed during routine treatment because the median incidence of complicated treatments during thermoneutral HD was approximately the same as that recorded during the screening phase of the study, when dialysate temperature was set according to the customary practice of each of the 27 centers participating in the study. Conversely, thermoneutral HD appears more appropriate as a control procedure because, at variance with standard HD, it allows us to evaluate the importance of body temperature changes independently from confounding effects of heat gain or loss through the extracorporeal blood circuit. A study design similar to ours was adopted in a recent investigation on the role of body temperature changes in hemodynamic response to HD treatment.[23]

A recent report, published after this trial had been completed, provides an important clue to better understand the relationship between body temperature and hemodynamics.[24,25] The investigators found that "with increasing ultrafiltration, more extracorporeal cooling is required to keep the dialysis patient at a constant temperature during hemodialysis and ultrafiltration." Their findings[25] support the volume hypothesis,[31] formulated originally by Gotch et al.[32] According to the hypothesis, acute blood volume contraction caused by the ultrafiltration process tends to elicit a sympathetically activated vasoconstrictive reaction in the peripheral circulation, especially in the cutaneous territory. This response may be associated with impairment of heat dissipation through the skin which, in conjunction with increased metabolic heat,[33] probably produced as a result of the sympathetic activation, leads to an increase in inner body temperature, thus eliciting peripheral vasodilatation. This tends to counteract and can even override the physiological (vasoconstrictive) response to volume contraction, eventually leading to a hypotensive crisis. Given that increase in core temperature is the significant factor predisposing to a hypotensive crisis, a corollary of the theory of Gotch et al[32] is that preventing the increase in body temperature is the crucial step to protect cardiovascular stability. This corollary is supported by our results.

One important drawback of our study is the lack of blinding of patients and nursing staff. However, double-blind trials are very difficult to organize for dialysis treatments that involve changes to the dialysis procedure, particularly if the intervention is based on changes to dialysate temperature, because in our experience, patients notice this change. The primary evaluation variable we chose for this study, ie, symptomatic hypotension so severe as to require immediate intervention, in our opinion, is robust enough to have minimized this drawback.

In summary, we conducted a clinical trial in a relatively large sample of appropriately selected patients under strictly controlled experimental

conditions. The study population consisted of a representative sample of patients known to be at high risk for recurrent dialysis hypotension, such as elderly patients, those with diabetes, and patients with various cardiovascular comorbidities. On this trial, we compared the effect on recurrent hypotension of a procedure aimed at preventing an increase in body temperature with a procedure aimed at preventing thermal energy transfer in the extracorporeal circulation. Results show that the former, in comparison with the latter procedure, resulted in a significant and clinically relevant reduction (50%) in recurrence of hypotensive episodes in HD sessions, whereas treatment efficacy remained unchanged. The clinical relevance of such a procedure may increase in the future if the trend toward an increasing proportion of high-risk patients in the new dialysis population continues.

APPENDIX

Participating centers include nephrology and dialysis departments of the following units: Belgium, St Jan Ziekenhuis, Brussels (G. van Roost); Czech Republic, Nemocnice Strahov, Prague (S. Sulková); Great Britain, St Helier Hospital, Carshalton (J.T.C. Kwan, M. Tacda); France, Hôpital Saint André, Bordeaux (C. Combe, C. Lasseur); Centre Hospitalier Lyon Sud, Pierre Bènite (M. Labeeuw); Centre Néphrologique d'Occitanie, Muret (R. Ibos); Hospices Civils, Strasbourg (T. Hannedouche, F. Chantrel); Centre Hospitalier Regional Bretonneau, Tours (J. Pengloan, B. Birmelé); Greece, Naval Hospital, Athens (I. Tsouras); Italy, Ospedale M. Malpighi, Bologna (A. Santoro, E. Mancini); Ospedale G. D'Annunzio, Chieti (L. Amoroso, A. Perilli); Ospedale S. Anna, Como (M. Fraticelli, L. Bernardi); Ospedale Provinciale di Circolo, Desio (G. Bonforte); Ospedale S. Maria Annunziata, Firenze (Q. Maggiore, F. Pizzarelli); Ospedale Maggiore, Lodi (E. Imbasciati, F. Malberti); Ospedale G. Melacrino e F. Bianchi, Reggio Calabria (C. Zoccali, M. Ciccarelli); Ospedale Civile, Sestri Levante (A. Magnasco); Ospedale Provinciale Civile, Sondrio (L. Pedrini, E. Filippini); Ospedale Regionale Maggiore, Trieste (G. Panzetta); The Netherlands, Medisch Spectrum Twente, Enschede (H. Brink); Portugal, FMC Dialysis Centre of Almada (P. Ponce, C. Santos); Instituto Portugues de Oncologia, Porto (A. Loureiro, J. Maximino); Hemodial, Vila Franca (A. Ferreira, M. Possante, C. Gil, C. Jorge); Hospital S. Pedro, Vila Real (T. Morgado, R. Castro); Spain, Hospital General, Albacete (C. Gomez Roldan, A. Serrano, E. Galliego, E. Gutiérrez, F. Liamas); Hospital General, Castellón (F. Maduell, J. Hernández, V. Cerillo); University Hospital Reina Sofia, Cordoba (A. Martín-Malo, P. Aljama, M.A. Álvarez de Lara, J. Hernadez, R. Crespo). Safety committee: P. Zucchelli (Ospedale M. Malpighi, Bologna, Italy), M. Surian (Ospedale Provinciale do Circolo, Desio, Italy), A. Albertazzi (Ospedale Regionale, Modena, Italy); Statistical analysis: D. Marcelli (Bad Homburg, Germany); Study coordination, A. Gauly (Bad Homburg, Germany).

ACKNOWLEDGMENT

The authors thank the staff at all centers that participated in this clinical study for their effort and all Fresenius Medical Care personnel in the various countries for their technical and logistical support.

REFERENCES

1. Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolò F, Parlongo S: Effect of extracorporeal blood cooling on dialytic arterial hypotension. Proc Eur Dial Transplant Assoc 18:597-602, 1981

2. Maggiore Q, Pizzarelli F, Sisca S, et al: Blood temperature and vascular stability during hemodialysis and hemofiltration. Trans Am Soc Artif Intern Organs 28:523-527, 1982

3. Pizzarelli F, Sisca S, Zoccali C, et al: Blood temperature and vascular stability in hemofiltration. Int J Artif Organs 6:37-41, 1983

4. Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolò F: Influence of blood temperature on vascular stability during hemodialysis and isolated ultrafiltration. Int J Artif Organs 8:175-178, 1985

5. Maggiore Q, Pizzarelli F, Sisca S, Catalano C, Delfino D: Vascular stability and heat in dialysis patients. Contrib Nephrol 41:398-402, 1984

6. Coli U, Landini S, Lucatello S, et al: Cold as cardiovascular stabilizing factor in hemodialysis: Hemodynamic evaluation. Trans Am Soc Artif Organs 29:71-75, 1983

7. 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 29:384-389, 1983

8. Sherman RA, Faustino EF, Bernholc AS, Eisinger RP: Effect of variations in dialysate temperature on blood pressure during hemodialysis. Am J Kidney Dis 4:66-68, 1984

9. Sherman RA, Rubin MP, Cody RP, Eisinger RP: Amelioration of hemodialysis-associated hypotension by the use of cool dialysate. Am J Kidney Dis 5:124-127, 1985

10. Lindholm T, Thysell H, Yamamoto Y, Forsberg B, Gullberg CA: Temperature and vascular stability in hemodialysis. Nephron 39:130-131, 1985

11. Kishimoto T, Yamamoto T, Shimuzu G, et al: Cardiovascular stability in low temperature dialysis. Dial Transplant 15:329-333, 1986

12. Provenzano R, Sawaya B, Frinak S, et al: The effect of cooled dialysate on thermal energy balance in hemodialysis patients. Trans Am Soc Artif Intern Organs 34:515-518, 1988

13. Marcen R, Orofino L, Quereda C, Pascual J, Ortuno J: Effect of cool dialysate in dialysis-related symptoms. Nephron 54:356-357, 1990

14. Orofino L, Marcen R, Quereda C, et al: Epidemiology of symptomatic hypotension in hemodialysis: Is cool dialysate beneficial for all patients? Am J Nephrol 20:177-180, 1990

15. Jost CMT, Agarwal R, Khair-El Din T, Grayburn PA, Victor RG, Henrich WL: Effects of cooler temperature dialysate on hemodialysis stability in "problem" dialysis patients. Kidney Int 44:606-612, 1993

16. Maggiore Q, Enia G, Catalano C, et al: Studies on hemodialysis hyperthermia. Blood Purif 2:125-129, 1984

17. Maggiore Q, Dattolo P, Piacenti M, et al: A pathophysiologic overview of dialysis hypotension. Contrib Nephrol 119:182-188, 1996

18. Maggiore Q, Dattolo P, Piacenti M, et al: Thermal balance and dialysis hypotension. Int J Artif Organs 18:518-525, 1995

19. Levin NW, Morris AT, Lavarias VA, et al: Effects of body core temperature reduction on hemodynamic stability and hemodialysis efficacy at constant ultrafiltration. Nephrol Dial Transplant 11:S31-S34, 1996 (suppl 2)

20. Schneditz D, Martin K, Kraemer M, Kenner T, Skrabal F: Effect of controlled extracorporeal blood cooling on ultrafiltration-induced blood volume changes during hemodialysis. J Am Soc Nephrol 8:956-964, 1997

21. Yu AW, Ing TS, Zabaneh RI, Daugirdas JT: Effect of dialysate temperature on central hemodynamics and urea kinetics. Kidney Int 48:237-243, 1995

22. Fine A, Penner B: The protective effect of cool dialysate is dependent on patients' predialysis temperature. Am J Kidney Dis 28:262-265, 1996

23. Kaufman AM, Morris AT, Lavarias VA, et al: Effects of controlled blood cooling on hemodynamic stability and urea kinetics during high-efficiency hemodialysis. J Am Soc Nephrol 9:877-883, 1998

24. Schneditz D: Temperature and thermal balance in hemodialysis. Semin Dial 14:357-364, 2001

25. Rosales LM, Schneditz D, Morris AT, Rahmati S, Levin NW: Isothermic hemodialysis and ultrafiltration. Am J Kidney Dis 36:353-361, 2000

26. van der Sande FM, Kooman JP, Burema JHGA, et al: Effect of dialysate temperature on energy balance during hemodialysis: Quantification of extracorporeal energy transfer. Am J Kidney Dis 33:1115-1121, 1999

27. Kraemer M, Polaschegg HD: Control of blood temperature and thermal energy balance during hemodialysis. Proc IEEE Engineering in Medicine and Biology 14th Annual International Conference, Paris, France, October 19-November 11, 1992

28. Harris J, Benedict F: A Biometric Study of Basal Metabolism in Man. Washington, DC, Carnegie Institution, publication no. 279, 1919

29. Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. J Am Soc Nephrol 4:1205-1213, 1993

30. Smye SW, Dunderdale E, Brownridge G, Will E: Estimation of treatment dose in high-efficiency haemodialysis. Nephron 67:24-29, 1994

31. Sherman RA: Advancing the cold front. Am J Kidney Dis 36:412-414, 2000

32. Gotch FA, Keen ML, Yarian SR: An analysis of thermal regulation in hemodialysis with one and three compartment models. Trans ASAIO 35:622-624, 1989

33. Ikizler TA, Wingard RL, Sun M, Harvel J, Parker RA, Hakim RM: Increased energy expenditure in hemodialysis patients. J Am Soc Nephrol 7:2646-2653, 1996