Relation between trends in body temperature and outcome in incident hemodialysis patients

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Abstract

Background. Various biochemical and physiological variables are related to outcome in hemodialysis (HD) patients. However, the prognostic implications of trends in body temperature (BT) in this population have not yet been studied. The aim of this study was to assess the relationship between trends in BT and outcome in incident HD patients.

Methods. Six thousand seven hundred and forty-two incident HD patients without thyroid disease from the Renal Research Institute were followed for 1 year. Patients were divided into tertiles of initial pre-dialysis BT (Tertile 1: ≤36.47°C, Tertile 2: >36.47 to 36.71°C and Tertile 3: >36.7°C) and further classified according to the change in BT (increased: >0.01°C/month, decreased: less than −0.01°C/month and stable, with change between −0.01 and +0.01°C/month) during the first year of treatment. The reference group is Tertile 2 of initial temperature with stable BT. Cox regression was used for survival analyses. Analyses were repeated for patients who survived the first year and were treated for ≥1 month in Year 2.

Results. BT decreased in 2903 patients, remained stable in 2238 patients and increased in 1601 patients. After adjustment for multiple risk factors, hazard ratios (HRs) for mortality were higher for those groups in whom, irrespective of the initial BT, BT increased or declined, as compared to the reference group during follow-up (HR between 1.46 and 2.27).

Conclusions. The best survival was observed in the group with the highest BT at baseline and stable BT during the follow-up period (HR 0.50).

Keywords: body temperature; epidemiology; outcomes; longitudinal

Introduction

Mortality in hemodialysis (HD) patients is high. Many prognostic factors have been identified in this patient population, most of them related to cardiovascular disease (CVD), inflammation or malnutrition. Other physiological variables, such as blood pressure, have also been found to be related to outcome in HD patients. However, this relationship appears to be complex, with both low and high blood pressures related to poorer outcome [1].

One important physiological variable which has received no attention so far as a marker of outcome in HD patients is body temperature (BT). However, in other diseases, such as acute heart failure and community-acquired pneumonia, a relation between low BT and adverse outcome was observed [2–4].

A frequent observation in the earlier days of dialysis therapy was a relatively low BT in uremic patients, so-called uremic hypothermia. The pathogenesis of this phenomenon is still uncertain; however, factors such as yet unidentified uremic cryogens and a reduced activity of Na–K-ATPase [5–7] have been implemented in its pathogenesis. In contrast to earlier studies [8, 9], a recent report showed a higher oral temperature in dialysis patients as compared to healthy controls, but determinants of BT were not assessed in detail [10].

There is abundant literature with regard to the relation between the acute intra-dialytic BT changes and the hemodynamic response during dialysis [11–13]. However, there is a paucity of data regarding the determinants of BT in HD patients, its long-term course and potential prognostic implications.

Aims of the present study were to identify prognostic implications of trends in BT in incident HD patients.

Materials and methods

Patient selection

The study population included 12 695 incident HD patients who started their incenter treatment between 1 January 2000 and 28 February 2010 in 51 facilities operated by the Renal Research Institute (RRI) and New York Dialysis Services (New York, NY). The clinics are primarily concentrated in New York State with some clinics located in North Carolina, Michigan, Connecticut, Illinois and California. Patients with data on demographic characteristics (date of birth, gender, race, ethnicity, diabetic status and height); patients with at least 13 treatments in the first year of HD; patients whose last treatment occurred within 30 days prior...
to discharge date or end of Year 1; patients who had > 50% of their treatments in the same dialysis shift and those with at least one albumin draw and urea kinetic modeling done in Year 1 were included (N=7003). Patients with thyroid disease were also excluded (n=261). Six thousand seven hundred and forty-two patients were included in the final analysis. Patients’ comorbid conditions were assessed using Center for Medicare and Medicaid Services (CMS) classification for comorbid conditions [14]. Patients who left the clinic, switched modality, received a transplant, were with the facility beyond the end of the observation period (28 February 2010) within the first year were censored; patients who survived the first year were also censored at 365 days. Time to death analysis was conducted for censored patients and those who died within the first 365 days of all-cause mortality.

Pre-dialysis BT (measured by appropriately trained health care professionals) was recorded in clinics prior to the start of each treatment; an average of pre-dialysis BT for the first 30 days of HD was computed per patient. The slope of pre-dialysis BT change was computed by linear regression using all temperature values in Year 1 or until censoring or death on a per patient basis irrespective of the P-value for the slope. Additional sensitivity analysis was conducted excluding first and last 12 temperature values in Years 1 and 2.

BTs are measured in all RRI clinics using two types of thermometers: 3M Tempa-Dot oral (3M) and Braun Welch Allyn (Welch Allyn) ear thermometers. In a previous study, we performed a validation study on the two types of thermometers [15]. Both temperature methods comply to ASTM (American Society for Testing and Materials) requirements. Maximum error is within 0.2°C for the Braun thermometer and within 0.1°C for the Tempa-Dot thermometer. For that study, the coefficient of variation (CV) in pre-dialytic temperature using the two devices was calculated. For the Tempa-Dot thermometer, a CV of 0.0086 (0.96%) was observed, whereas the CV was 0.0086 (0.86%) for the Braun thermometer. The same thermometer model is used within each clinic; therefore, the analysis of pre-dialysis BTs is adjusted by clinic to account for this difference. Dialysis temperature and composition was kept constant during the observation period.

Room temperature in the clinics is climate controlled but may sometimes be slightly adjusted in response to preferences of patients and/or staff. Thus, some variability between clinics is possible given clinic specific policies within federal regulations (section V.405 of Centre for Medicare and Medicaid services; end-stage renal disease interpretative guidance section 1.1, dated 4 October 2008). However, this variability is accounted for by adjustment by clinic.

RRI follows ultrapure Association for the Advancement of Medical Instrumentation (AAMI) standards in water and dialyzate quality. As such, all clinics studied achieved between 80 and 100% of the dialyzate Limulus amebocyte lysate (LAL)<0.03. However, it should be noted that data on LAL and dialyzate cultures are only available in the database since 2008. Given the fact that pre-dialysis BT, and not intra-dialytic changes were studied, results for microbiological dialyzate quality are not included in the analysis.

Patients were stratified according to the tertiles of pre-dialysis BT in the first 30 days (Tertile 1: ≥ 36.47°C, Tertile 2: > 36.47°C and 36.71°C and Tertile 3: > 36.7°C) and according to the temperature slope (increased: > 0.01°C/month, decreased: less than −0.01°C/month and stable, with change between −0.01 and +0.01°C/month). This resulted in nine distinct groups based on starting pre-dialysis temperature and slopes.

Other repeated measures such as pre-dialysis systolic and diastolic blood pressures (pre-SBP and pre-DBP, respectively), inter-dialytic weight gain (IDWG), post-dialysis weight, albumin, equilibrated normalized protein catabolic rate (enPCR), eKdrt/V and creatinine were computed as an average of all values in the first year or until censoring or death. All labs were measured by Spectra Laboratories (Rockleigh, NJ). Total neutrophil count, as a surrogate parameter of inflammation [16], was available on a monthly basis in 64% of the population.

To validate our findings, we conducted an analysis of patients who survived up to the beginning of the second year of HD. We repeated our methodology by stratifying the patients according to the BTs in the first 30 days of Year 2 and according to the BT slope in the second year.

This analysis of the RRI database was approved by the Beth Israel Medical Center IRB.

### Statistical analysis

The nine pre-dialysis BT and BT slope groups were compared using analysis of variance. Similar comparison was conducted for three groups of baseline BT and three groups of BT slopes. Mortality analysis was conducted using unadjusted Kaplan–Meier analysis as well as Cox proportional hazards model adjusted for gender, age, race, ethnicity, comorbid conditions, body mass index (BMI), pre-SBP and pre-DBP, IDWG, post-dialysis weight, inter-dialytic volume, albumin, enPCR, eKdrt/V, creatinine, residual renal function, access type, individual clinic, season in which patient started treatment and dialysis shift. In a subgroup analysis, an adjustment for the slope in total neutrophil count was performed.

All P-values are two sided. The analyses were conducted in SPSS version 18 (IBM, Somers, NY) and SAS version 9.2 (SAS Institute, Cary, NC).

### Results

#### Demographics

Six thousand seven hundred and forty-two patients with an average age of 62.1 (SD 15.5) years were studied. Patient characteristics are displayed in Table 1. Overall, patients started with an average BT of 36.57°C and experienced a drop of 0.009°C/month.

#### Relation between baseline BT, comorbid conditions and other patient characteristics

Patients who started with lower BTs (Tertile 1) were more likely to experience an increase in their BT (average increase: 0.006°C/month), while patients who started with higher BTs were more likely to experience a decline in BT in the first year (average decline: 0.023°C/month). In an analysis of demographic characteristics, patients with higher BTs were more likely to be female (46%), younger (58.3 years), twice more likely to be of Black race than patients with lower BTs (53 versus 27%) and more likely to be of Hispanic ethnicity (Table 1). In an analysis of comorbid conditions, patients with higher starting BTs compared to patients in Tertile 1 were less likely to have arthrythmias, cerebrovascular disease, cancer, congestive heart failure (CHF), ischemic heart disease and chronic obstructive pulmonary disease, whereas a lower percentage had a history of myocardial infarction and peripheral vascular disease/peripheral arterial disease. At the same time, patients with higher BTs were more likely to have HIV/AIDS than patients with lower BTs (Table 1).

Patients with higher starting BTs are also more likely to be larger (average BMI 28.4 kg/m²), have higher pre-SBP and pre-DBP (150.8 and 79.6 mmHg, respectively), have higher albumin (3.72 g/dL), higher creatinine (7.98 g/dL), less likely to have residual renal function at the start of HD (29%) and slightly less likely to have catheters at the start of HD (71%) (Table 1).

#### Relation between change in BT, comorbid conditions and other patient characteristics

Two thousand and ninety-three patients experienced a decline in BT (43%); 2238 patients remained steady (33%) and 1601 experienced an increase in BT (24%). In an analysis of demographic characteristics, patients whose BT increased were more likely to be male (61%). Patients with stable BTs were more likely to be of Black
race. Notably, no significant differences existed in age and ethnicity between groups of BT patterns (Table 2).

In an analysis of comorbid conditions, patients with stable BTs compared to the other two groups were less likely to have arrhythmias and CHF. Patients with stable BTs were also more likely to have higher pre-SBP and pre-DBP (150.2 and 77.8 mmHg), have higher IDWG (3.2 %), have higher albumin (3.75 g/dL), higher nPCR (0.87 g/kg/day), higher creatinine (7.53 mg/dL) and more likely to have residual renal function at the start of dialysis (36 %) (Table 2).

Relation between BT changes and survival

The relation between changes in BT and outcome is displayed by a Kaplan–Meier plot (Figure 1). Cox proportional hazards model adjusted for multiple covariates demonstrated that patients with stable BTs have better outcomes, while patients with increasing BTs have poorest outcomes in the first year of dialysis (Table 3). In the three ranges of BT patterns (decliners, stable and increasers), patients with highest beginning BTs had the best outcomes [hazard ratios (HRs) of 1.46, 0.50 and 2.03, respectively] followed by patients in Tertile 1 (HRs of 1.73, 0.96 and 2.18, respectively) (Figure 2).

These data were confirmed by an analysis of patients in the second year after starting dialysis treatment, which showed comparable results as the first year after starting dialysis (Figure 3). Also, a subgroup analysis in patients in whom total neutrophil counts were available showed no material changes in HRs after adjustment for the change in neutrophil count (HR in patients with declining temperature were 2.69, 2.07 and 1.97 in temperature Tertiles 1, 2 and 3, respectively; in patients with increasing temperature, HRs were 3.16, 3.24 and 2.25 in temperature Tertiles 1, 2 and 3, respectively).

In an analysis of causes of deaths in the nine groups, patients who started with lower BTs were more likely to

### Table 1. Patient characteristics—by beginning BT

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1 (≤ 36.47°C)</th>
<th>Tertile 2 (&gt; 36.47 to 36.71°C)</th>
<th>Tertile 3 (&gt; 36.7°C)</th>
<th>Total</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2251</td>
<td>2250</td>
<td>2241</td>
<td>6742</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pre-dialysis temperature slope (per month)</td>
<td>0.007 (0.072)</td>
<td>−0.009 (0.051)</td>
<td>−0.023 (0.063)</td>
<td>−0.009 (0.064)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pre-dialysis temperature at baseline (t)</td>
<td>36.2 (0.26)</td>
<td>36.6 (0.07)</td>
<td>36.9 (0.18)</td>
<td>36.57 (0.34)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Male</td>
<td>60</td>
<td>58</td>
<td>54</td>
<td>57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age</td>
<td>65.7 (15.3)</td>
<td>61.7 (15.3)</td>
<td>58.3 (15.1)</td>
<td>61.9 (15.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Race % Black</td>
<td>27</td>
<td>38</td>
<td>53</td>
<td>39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% White</td>
<td>65</td>
<td>54</td>
<td>38</td>
<td>52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Asian</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.028</td>
</tr>
<tr>
<td>Ethnicity % Hispanic</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Comorbid % Diabetic</td>
<td>56</td>
<td>54</td>
<td>51</td>
<td>54</td>
<td>0.033</td>
</tr>
<tr>
<td>% With cancer (other than skin)</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With cardiac dysrhythmias</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With cerebrovascular disease</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With CHF</td>
<td>17</td>
<td>11</td>
<td>9</td>
<td>12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With COPD</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>0.003</td>
</tr>
<tr>
<td>% With HIV or AIDS</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With hyperparathyroidism</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.003</td>
</tr>
<tr>
<td>% With infection</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With ischemic heart disease</td>
<td>13</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With MI (incl cardiac arrest)</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.006</td>
</tr>
<tr>
<td>% With PVD or PAD</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27 (9.5)</td>
<td>27.9 (10.8)</td>
<td>28.4 (9.2)</td>
<td>27.8 (9.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pre-dialysis SBP</td>
<td>146.9 (18.8)</td>
<td>149.5 (17.9)</td>
<td>150.8 (17.5)</td>
<td>149.1 (18.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pre-dialysis DBP</td>
<td>75.2 (11.1)</td>
<td>77.8 (10.8)</td>
<td>79.6 (10.6)</td>
<td>77.5 (10.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IDWG (% of post-dialysis weight)</td>
<td>3.17</td>
<td>3.16 (0.98)</td>
<td>3.15 (0.96)</td>
<td>3.16 (0.99)</td>
<td>0.75</td>
</tr>
<tr>
<td>Post-dialysis weight</td>
<td>75.1 (20.2)</td>
<td>77.1 (20.6)</td>
<td>78.6 (21.4)</td>
<td>77 (20.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urea distribution volume</td>
<td>39 (8.3)</td>
<td>40 (8.9)</td>
<td>40.4 (9.2)</td>
<td>3.71 (0.43)</td>
<td>0.004</td>
</tr>
<tr>
<td>enPCR</td>
<td>0.85 (0.21)</td>
<td>0.86 (0.2)</td>
<td>0.85 (0.2)</td>
<td>0.86 (0.21)</td>
<td>0.074</td>
</tr>
<tr>
<td>eKdrt/V</td>
<td>1.4 (0.35)</td>
<td>1.38 (0.29)</td>
<td>1.35 (0.29)</td>
<td>1.38 (0.31)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6.66 (2.48)</td>
<td>7.35 (2.72)</td>
<td>7.98 (2.84)</td>
<td>7.33 (2.74)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With residual renal function at baseline</td>
<td>35</td>
<td>36</td>
<td>29</td>
<td>33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% With arteriovenous fistula at start of dialysis</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.473</td>
</tr>
<tr>
<td>% With arteriovenous graft at start of dialysis</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>0.003</td>
</tr>
<tr>
<td>% With catheters at start of dialysis</td>
<td>74</td>
<td>73</td>
<td>70</td>
<td>72</td>
<td>0.016</td>
</tr>
<tr>
<td>% With Temp-Dot thermometers</td>
<td>84</td>
<td>90</td>
<td>94</td>
<td>89</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Treated in morning</td>
<td>30</td>
<td>27</td>
<td>26</td>
<td>28</td>
<td>0.007</td>
</tr>
<tr>
<td>% Treated in afternoon</td>
<td>32</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>0.044</td>
</tr>
<tr>
<td>% Treated in evening</td>
<td>6</td>
<td>12</td>
<td>16</td>
<td>11</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PVD, peripheral vascular disease; PAD, peripheral arterial disease.
die of cardiovascular reasons than other patients. Patients who started with higher BTs (Tertile 3) were more likely to die of infections or neoplasms; notably, 11% of patients who started with BT > 36.71°C and declined died of neoplasms, which is significantly higher than the overall population where only 5% of patients died of neoplasms. In patients who started with normal BTs (36.47 to 36.71°C), distribution of causes of deaths varied greatly across patterns of BT; patients whose temperature remained steady were more likely to die of CVD causes (75% compared to overall population of 61%), while patients whose BT increased in the first year were more likely to die of infection-related causes (29% compared to overall population of 14%) (Table 4).

In an analysis of temporal trends of BT before death, we observed that declines and increases in BT appear to be a more chronic, long-term phenomena, rather than acute decrease or increase immediately preceding death. We assessed this relationship by fitting different curves to BTs before death and linear relationship described it with highest $r^2$ (Figure 4 and 5).

**Discussion**

The main finding of the present study is the association between trends in pre-dialytic BT and outcome in chronic HD patients. The highest mortality was observed in the cohorts in whom BT increased or decreased during the follow-up period, irrespective of the baseline BT at baseline. The lowest mortality was observed in the group with the highest BT at baseline and with stable BTs during the follow-up period. To the best of our knowledge, this is the first study in which the relation between BT and outcome was studied in HD patients. Moreover, as compared to many epidemiological studies in dialysis patients, this

<table>
<thead>
<tr>
<th>N</th>
<th>Pre-dialysis temperature slope (per month)</th>
<th>Pre-dialysis temperature at baseline (°C)</th>
<th>% Male</th>
<th>Age</th>
<th>Race</th>
<th>Ethnicity</th>
<th>Comorbid</th>
<th>BMI</th>
<th>Pre-dialysis SBP</th>
<th>Pre-dialysis DBP</th>
<th>IDWG (% of post-dialysis weight)</th>
<th>Post-dialysis weight</th>
<th>Urea distribution volume</th>
<th>Albumin</th>
<th>eKdrt/V</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declined (drop less than −0.01°C/month)</td>
<td>2903</td>
<td>36.65 (0.33)</td>
<td>56</td>
<td>61.7 (15.4)</td>
<td>53</td>
<td>% Black</td>
<td>% Diabetic</td>
<td>7.31 (2.77)</td>
<td>149.1 (18.3)</td>
<td>77.8 (11)</td>
<td>3.13 (1)</td>
<td>76.6 (20.6)</td>
<td>39.7 (8.9)</td>
<td>3.68 (0.45)</td>
<td>1.37 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Steady (change −0.01 to 0.01°C/month)</td>
<td>2238</td>
<td>36.58 (0.29)</td>
<td>57</td>
<td>61.8 (15.4)</td>
<td>49</td>
<td>% White</td>
<td>% With cancer (other than skin)</td>
<td>7.53 (2.7)</td>
<td>150.2 (17.7)</td>
<td>77.8 (10.6)</td>
<td>3.21 (0.94)</td>
<td>77.4 (20.9)</td>
<td>39.7 (8.8)</td>
<td>3.75 (0.39)</td>
<td>1.38 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Increased (increase ≥0.01°C/month)</td>
<td>1601</td>
<td>36.39 (0.37)</td>
<td>61</td>
<td>62.5 (15.9)</td>
<td>57</td>
<td>% Asian</td>
<td>% With cardiac dysrhythmias</td>
<td>7.12 (2.72)</td>
<td>147.4 (18.4)</td>
<td>76.7 (11.3)</td>
<td>3.13 (1.03)</td>
<td>77.2 (20.9)</td>
<td>40.1 (8.8)</td>
<td>3.68 (0.46)</td>
<td>1.38 (0.36)</td>
<td></td>
</tr>
<tr>
<td>Total P-values</td>
<td>6742</td>
<td>36.75 (0.34)</td>
<td>57</td>
<td>61.9 (15.5)</td>
<td>52</td>
<td>% Hispanic</td>
<td>% With CHF</td>
<td>7.33 (2.74)</td>
<td>149.1 (18.1)</td>
<td>77.5 (10.9)</td>
<td>3.16 (0.99)</td>
<td>77.2 (20.8)</td>
<td>39.8 (8.8)</td>
<td>3.71 (0.43)</td>
<td>1.38 (0.31)</td>
<td></td>
</tr>
</tbody>
</table>

*CopD, chronic obstructive pulmonary disease; MI, myocardial infarction; PVD, peripheral vascular disease; PAD, peripheral arterial disease.
BT trends and survival in HD

Fig. 1. Survival by BT slope.

Table 3. Cox proportional hazards results for Year 1 (only significant predictors are shown)*

<table>
<thead>
<tr>
<th>HR</th>
<th>Lower</th>
<th>Upper</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1, declined</td>
<td>1.731</td>
<td>1.185</td>
<td>2.528</td>
</tr>
<tr>
<td>Tertile 2, declined</td>
<td>1.766</td>
<td>1.232</td>
<td>2.532</td>
</tr>
<tr>
<td>Tertile 3, declined</td>
<td>1.463</td>
<td>1.025</td>
<td>2.088</td>
</tr>
<tr>
<td>Tertile 1, stable</td>
<td>0.962</td>
<td>0.625</td>
<td>1.481</td>
</tr>
<tr>
<td>Tertile 2, stable</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 3, stable</td>
<td>0.500</td>
<td>0.286</td>
<td>0.874</td>
</tr>
<tr>
<td>Tertile 1, increased</td>
<td>2.175</td>
<td>1.531</td>
<td>3.089</td>
</tr>
<tr>
<td>Tertile 2, increased</td>
<td>2.265</td>
<td>1.524</td>
<td>3.366</td>
</tr>
<tr>
<td>Tertile 3, increased</td>
<td>2.028</td>
<td>1.223</td>
<td>3.361</td>
</tr>
<tr>
<td>Male</td>
<td>1.350</td>
<td>1.089</td>
<td>1.673</td>
</tr>
<tr>
<td>Age</td>
<td>1.020</td>
<td>1.012</td>
<td>1.029</td>
</tr>
<tr>
<td>Infection</td>
<td>0.402</td>
<td>0.198</td>
<td>0.816</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0.588</td>
<td>0.396</td>
<td>0.873</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.174</td>
<td>1.086</td>
<td>4.352</td>
</tr>
<tr>
<td>Pre-dialysis SBP</td>
<td>0.983</td>
<td>0.976</td>
<td>0.991</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.201</td>
<td>0.167</td>
<td>0.242</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.835</td>
<td>0.789</td>
<td>0.885</td>
</tr>
<tr>
<td>Residual renal function at baseline</td>
<td>0.486</td>
<td>0.375</td>
<td>0.629</td>
</tr>
<tr>
<td>AVG at start of dialysis</td>
<td>0.672</td>
<td>0.453</td>
<td>0.997</td>
</tr>
<tr>
<td>Treated in other shift</td>
<td>1.376</td>
<td>1.070</td>
<td>1.771</td>
</tr>
<tr>
<td>Treated in evening shift</td>
<td>2.092</td>
<td>1.507</td>
<td>2.903</td>
</tr>
</tbody>
</table>

*Other covariates in the model omitted with P > 0.05: White race, Asian race, Hispanic ethnicity, diabetes, anemia, cancer, cardiac dysrhythmias, cerebrovascular disease, CHF, chronic obstructive pulmonary disease, drug or alcohol dependence, gastrointestinal bleeding, hepatitis, HIV/AIDS, hyperparathyroidism, peripheral vascular disease/peripheral arterial disease, pneumonia, BMI, IDWG, post-dialysis weight, pre-dialysis DBP, urea distribution volume, enPCR, treated in afternoon shift, started in spring, summer or fall and clinic location. Reference group: race = Black; ethnicity = non-Hispanic; access type = catheter; treated in morning shift; started dialysis in winter. Sig., significance.

analysis is not only cross-sectional but also takes longitudinal trends into account.

BT at baseline appeared to be related to various factors. The tertile with the lowest BT was characterized by a higher percentage of males and white patients and higher age, where nutritional parameters, such as BMI and serum creatinine, were lower as compared to the reference group. Moreover, the relative percentage of patients with various comorbid conditions was higher in the lowest tertile. This is in contrast to studies in animal models, in which low BTs were related to longevity [17].

Patients with higher starting BTs appeared to be more likely to experience a decline in their temperature in the first year, while patients with the lower BTs experienced an increase in their temperature, raising the possibility of ‘regression to the mean’ phenomenon. Although this is a possibility, this is unlikely because of the associated higher mortality in these groups as well as because the results were similar in the second year. Interestingly, there was an average decline in BT in the entire population possibly brought about by a change in inflammatory status due to initiation of HD.

The percentage of patients with ‘uremic hypothermia’ at baseline cannot be deduced from the study due to the absence of a control group with healthy subjects. However, mean values for the cohort do not appear to differ widely from values reported in the literature for the general population [18], although timing of the measurements was variable in our study, depending on the dialysis shift. Notably, residual renal function was highest in the middle and not in the highest tertile.

The results of the present study suggest that a lower pre-dialytic BT might be, to some degree, a marker of comorbidity but is also related to other factors, such as age, race and BMI. In a multivariate analysis gender, age, race as well as various comorbid conditions were all significant predictors of BT. The lower BT in males as compared to females and the inverse relation between age and temperature are in agreement with data from the general population [19, 20]. However, in the general population, the relation between BMI and BT is controversial. Whereas some studies found BMI to be inversely related to BT [19], others observed either no relationship [21] or a positive relation between BMI and BT [22].

Despite the relation with comorbidity, in the Cox regression model, baseline pre-dialytic BT did not appear to emerge as a powerful independent risk factor, although the data of this study suggest that mortality is lowest in the group with the highest pre-dialytic BT at baseline. Trends for BT appeared to be more strongly related to outcome than baseline temperature per se. This held true for an increasing as well as a decreasing trend, which was independently associated with an increased risk for mortality, independently of baseline BT.

When dividing the study group within three cohorts depending on the trend in BT, the cohort with the increase in BT was characterized by a lower serum albumin as well as lower serum creatinine levels as compared to the group with stable BT, which might point at a malnourished or inflammatory state or both. Although C-reactive protein levels were not assessed, it might be hypothesized that the increase in BT could be explained by a stimulation of the acute-phase response [23].

More intriguing appears to be the fact that the groups with a decreasing temperature had an increased risk of
mortality as compared to the groups with stable BT. Characteristics for the group in whom BT declined during the follow-up period were comparable to the group with an increase in BT, which is congruent with a U-shaped phenomenon. With the parameters used in the present analysis, we were not able to establish parameters which could predict why patients experience a decline as compared to an increase in BT. In an analysis of trends in BT before death, we observed that declines and increases in BT appear to be a more chronic, long-term phenomena,
rather than acute drop or increase immediately preceding death. This held true for both patient groups with an increase as well as a decrease BT before death.

Thus, the causes behind the relation between the decline in BT and adverse outcome cannot be deduced from the present data. It has been hypothesized that a reduction in BT might be an adaptive response of the body to inflammation when the body cannot cope with the increasing demands of fever, e.g. in cases of insufficient nutrition [24]. This might coincide with the non-thyroidal illness syndrome, characterized by a lowering of the metabolic state and reduction of T3 levels [25]. Recently, a relation between low free T3 levels and mortality was observed in dialysis patients [26].

Several cryogenic factors, such as melanocyte-stimulating hormone (MSH) and neuropeptide Y as well as a reduced Na–K–ATPase activity, which may be influenced by both renal failure as well as inflammation, might play a role in changes in core temperature in dialysis patients [23–25, 27–31]. However, the role of these putative factors should be assessed in future studies.

Another factor that might lead to a decrease in BT is cardiac failure. Low BT was associated with increased mortality in patients with heart failure [2, 3, 32], but mortality from cardiac causes did not appear to be different between the subgroups of patients with increasing or lowering trends, although mortality from infectious causes was higher in one subgroup of patients with an increase in BT.

Lastly, though unlikely, a contributing effect of low ambient temperatures on both BT and outcome should be discussed. Ambient temperature likely has an effect on BT [33], whereas higher mortality in winter period was recently shown by our group in dialysis patients and also in the general population [34, 35]. However, the relation between trends and BT remained significant after correction for season. Moreover, when looking at the trends in BT, a gradual increase or decrease in BT was observed in those patients who expired during the study period.

A major strength of this analysis is the large sample size and patients treated in 51 different dialysis clinics in different states and geographical regions. Widespread patient population and the considerably large sample size, the study cohort may be assumed generalizable to the HD population in the USA. Selection of incident patients allowed the study of the evolution of BT virtually without effects of HD treatment at study baseline. Although the results may not have an immediate impact on daily patient care, we suggest that they are of considerable interest, by showing that the dynamics of key physiological parameters in dialysis patients are profoundly related to mortality. The concept regarding longitudinal trends and mortality is relatively novel in dialysis patients and might

| Tertile 1, declined | 57 | 13 | 5 | 25 |
| Tertile 2, declined | 55 | 14 | 5 | 26 |
| Tertile 3, declined | 55 | 16 | 11* | 18 |
| Tertile 1, steady | 69 | 5 | 0 | 26 |
| Tertile 2, steady | 75* | 6 | 4 | 15 |
| Tertile 3, steady | 56 | 11 | 11 | 22 |
| Tertile 1, increased | 68 | 13 | 3 | 16 |
| Tertile 2, increased | 55 | 29* | 2 | 14 |
| Tertile 3, increased | 58 | 19 | 4 | 19 |
| Overall population | 61 | 14 | 5 | 20 |

*P < 0.05 comparing given percentage with overall population.

Fig. 4. Mean weekly BTs prior to death in patients whose BTs declined.
find future clinical application as part of a multidimensional risk model in this vulnerable group of patients.

Drawbacks of the study are firstly the use of two different methods which were used to assess BT. However, the method used had no impact on the relation between temperature trends and mortality after inclusion in the Cox model after adjusting by clinic. Second, timing of the BT measurement as well as ambient temperature can also have important effects on BT. However, additional consideration of these factors, by adjustment for geographical location, timing of dialysis shift and season of start dialysis, in the Cox model did not materially alter the results. Moreover, no detailed data of inflammation were available, except for serum albumin, which was lower in the cohorts with both a reduction and an increase in BT during the follow-up period. No information on T3 levels which may influence temperature was available.

Conclusions

During a 1-year follow-up period, both an increasing as well as a declining trend in BT was associated with an increased risk of death in incident HD patients. Prognosis was best in patients in the highest tertile for baseline BT, which remained stable during the follow-up period. Trends in BT appear to be a marker for outcome in HD patients. More detailed analysis of BT changes is needed to obtain more insight into the pathophysiological mechanisms behind trends in BT and mortality in HD patients.

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References


Fig. 5. Mean weekly BTs prior to death in patients whose BTs increased.
Vasopressin release is enhanced by the Hemocontrol biofeedback system and could contribute to better haemodynamic stability during haemodialysis

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Abstract

Background. Haemodialysis with the Hemocontrol biofeedback system (HHD) is associated with improved haemodynamic stability compared with standard haemodialysis (HD) (SHD). Although the beneficial effect of HHD on haemodynamic stability is generally explained by its effect on blood volume, we questioned whether additional factors could play a role. Since HHD is associated with higher initial dialysate sodium concentrations and ultrafiltration (UF) rate, we studied whether the