Accidental hypothermia and active rewarming: the metabolic and inflammatory changes observed above and below 32°C

J J McInerney, A Breakell, W Madira, T G Davies, P A Evans

Objectives: In accidental hypothermia the underlying physiological mechanisms responsible for poor outcome during rewarming through 32°C remain obscure, although possible associations include changes in acid-base balance, divalent cations, and inflammatory markers. This study investigated the metabolic and inflammatory changes that occur during the rewarming of hypothermic patients.

Methods: Eight patients, four men and four women, age 45 to 85 years, admitted with core temperatures <35°C were included in the study. Patients were rewarmed with dry warm blankets and fluid replaced by crystalloid at 40°C. Bloods for pH, ionised calcium (Ca²⁺) and magnesium (Mg²⁺), parathyroid hormone (PTH), interleukin 1 (IL1), interleukin 6 (IL6), tissue necrosis factor α (TNFα), were collected at presentation, during rewarming, and at 24 hours.

Results: Four patients were admitted with mild (32°–35°C) and four with moderate (28°–32°C) hypothermia. Rewarming to 32°C had no significant effect on the presenting acidosis (p=0.1740), although above 32°C pH increased with temperature (p<0.0001). There was a negative correlation between pH and both Ca²⁺ (p=0.0005) and Mg²⁺ (p=0.0488) below 32°C; above this temperature the relation was significant only for Ca²⁺ (p=0.0494). PTH and Ca²⁺ correlated positively (p=0.0041) and negatively (p=0.0039) below and above 32°C respectively. There was no relation between IL1 or TNFα with Ca²⁺ during rewarming, but IL6 and Ca²⁺ correlated positively (p=0.0039) and negatively (p=0.0018) when presentation temperature was below and above 32°C respectively.

Conclusions: During rewarming pH remains unchanged until patient temperature approaches 32°C. Ca²⁺ and Mg²⁺ decline is associated with the pH increase above 32°C. Poor outcome is associated with presentation temperature (<32°C), non-physiological correlation between IL6-PTH-Ca²⁺, and age (≥84 years).

Accidental hypothermia (core temperature <35°C) although uncommon, is associated with a significant and increasing mortality rate. Patients presenting with mild hypothermia (32°C–35°C) generally do better than those with moderate (28°C–32°C) or severe (<28°C) hypothermia. The mechanisms contributing to mortality are not well understood, but the metabolic changes associated with hypothermia include: acidosis, changes in plasma ionised calcium (Ca²⁺), and the efflux of magnesium (Mg²⁺) and potassium (K⁺) from intracellular to extracellular fluid.

The control of plasma ionised calcium by parathyroid hormone (PTH) in health is well established. PTH may also be of prognostic value in critical illness, with a dissociation of the inverse physiological relation with Ca²⁺ in cardiac surgery patients, suggesting that changes in ionised calcium are not always entirely pH dependent. PTH regulation of plasma ionised calcium is mediated by interleukin 6 (IL6).

Hypothermia has been shown to be associated with alterations in IL6 and the other proinflammatory cytokines, interleukin 1 (IL1), and tissue necrosis factor α (TNFα), which stimulate release of acute phase proteins. This study investigated the effect of the severity of hypothermia (mild or moderate) on the relation between pH, Ca²⁺, Mg²⁺, PTH, IL6, IL1, and TNFα during rewarming.

METHODS

Patients with accidental hypothermia (core temperatures <35°C) presenting to the accident and emergency department were included in the study. Patients who had suffered major trauma or excessive blood loss, and who would require significant fluid resuscitation were not included. Ethical approval was granted by the Leicestershire Ethics Committee. Patient temperatures were measured by means of the First Genius Tympanic Thermometer, which has been shown to accurately measure core temperature. All patients were assessed and treated along recognised Advance Life Support (ALS) guidelines. Patients were undressed and covered in warm blankets, which were changed frequently. Core temperature was reassessed at 15 minute intervals to ensure optimal rate of rewarming. Maintenance intravenous fluids when administered, were in the form of normal saline, dextrose saline or 5% dextrose solutions pre-warmed to 40°C. No patient received supplemental calcium, magnesium or potassium.

Blood for the determination of Ca²⁺ and Mg²⁺ was collected following the recommendations of Boink et al, with venous samples for the immediate measurement of Ca²⁺ (reference range 1.1–1.3 mmol/l), Mg²⁺ (reference range 0.53–0.67 mmol/l), and pH (by AVL 988–4 analyser) collected into dry heparin tubes. There was no correction made for temperature. Arterial blood gas analysis was also undertaken in each patient. Venous blood was also collected for later measurement of PTH, IL6, IL1, and TNFα by quantitative sandwich enzyme immunoassay technique (QuantiKine, R&D systems).

Abbreviations: PTH, parathyroid hormone; IL1, interleukin 1; IL6, interleukin 6; TNFα; tissue necrosis factor α.
Serial serum samples were collected throughout the rewarming phase (at +1°C increments) and at 24 hours.

Venous samples for later routine laboratory measurement of urea and electrolytes, thyroid function tests, cardiac enzymes, amylase, and full blood count were collected into serum gel and EDTA tubes as appropriate. All patients had 12 lead electrocardiograms (ECG) at presentation and at 24 hours.

**Statistical methods**

Standard least squares regression was used, and significance was assessed using the correlation coefficient ($r$). Regression coefficients were compared using a $t$ test.$^{24}$

**RESULTS**

Over an eight month period, four men and four women with a mean age of 74.3 years (range 45–85) were included in the study. A variety of medical conditions were associated with the presentation of accidental hypothermia, namely pneumonia, urinary tract infection, drug overdose, epilepsy, and ischaemic heart disease.

Four patients presented with moderate (28°C–32°C) and the remainder with mild hypothermia (32°C–35°C). All patients with moderate hypothermia were aged 84 years or over and died within seven days of admission. Those with mild hypothermia were all aged less than 84 years and survived to discharge (table 1).

The mean rate of initial re-warming was 0.78°C/hour with a range of 0.4–1.5°C/hour. All patients responded to treatment with an increase in core temperature over time (fig 1). Patients received normal maintenance fluid in the form of crystalloids with an increase in core temperature over time (fig 1). Patients had abnormal ECG at presentation, two with classic J waves and five with atrial fibrillation (rates between 50–120). No patient received antiarrhythmia drug therapy. Of the patients with atrial fibrillation one reverted spontaneously to sinus rhythm, and two to a normal pulse rate. There was no significant change in plasma potassium concentration in any patient during the 24 hour study period despite changes in acid-base balance. All patients except one had increased plasma creatine

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### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Admission core temperature (°C)</th>
<th>Pulse beats/min</th>
<th>Blood pressure mm Hg</th>
<th>Glasgow Coma Score</th>
<th>Admission ECG</th>
<th>24 hour ECG</th>
<th>Outcome</th>
<th>Admission length</th>
<th>Associated diseases*</th>
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<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>M</td>
<td>32.4</td>
<td>62</td>
<td>130/80</td>
<td>7</td>
<td>J waves</td>
<td>Sinus rhythm</td>
<td>Survived</td>
<td>1 day</td>
<td>Chlordiazepoxide overdose</td>
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<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>32.8</td>
<td>56</td>
<td>130/50</td>
<td>15</td>
<td>Slow AF</td>
<td>Sinus rhythm</td>
<td>Died</td>
<td>22 days</td>
<td>Epileptic seizure</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>F</td>
<td>30.8</td>
<td>70</td>
<td>140/50</td>
<td>15</td>
<td>AF</td>
<td>Sinus rhythm</td>
<td>Died</td>
<td>4 days</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>M</td>
<td>31.3</td>
<td>60</td>
<td>110/60</td>
<td>15</td>
<td>AF/BBB</td>
<td>–</td>
<td>Died</td>
<td>&lt;1 day</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>F</td>
<td>32.2</td>
<td>80</td>
<td>140/90</td>
<td>7</td>
<td>J waves</td>
<td>Sinus rhythm</td>
<td>Survived</td>
<td>7 days</td>
<td>Diazepam overdose</td>
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<td>6</td>
<td>73</td>
<td>F</td>
<td>34.9</td>
<td>70</td>
<td>170/80</td>
<td>7</td>
<td>Sinus rhythm</td>
<td>Sinus rhythm</td>
<td>Survived</td>
<td>8 days</td>
<td>Urinary tract infection</td>
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<tr>
<td>7</td>
<td>84</td>
<td>M</td>
<td>29.0</td>
<td>50</td>
<td>110/50</td>
<td>7</td>
<td>Slow AF</td>
<td>AF</td>
<td>Died</td>
<td>7 days</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>F</td>
<td>28.4</td>
<td>120</td>
<td>100/70</td>
<td>7</td>
<td>AF</td>
<td>–</td>
<td>Died</td>
<td>&lt;1 day</td>
<td>Myocardial infarction</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; AF, atrial fibrillation; LBBB, left bundle branch block. *As determined clinically, includes precipitating causes.
### Table 2
Baseline biochemical measurements of the eight patients in the study

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/sex</th>
<th>Sodium (133–144) mmol/l</th>
<th>Potassium (3.3–5.3) mmol/l</th>
<th>Urea (2.5–6.5) mmol/l</th>
<th>Creatinine (60–120) µmol/l</th>
<th>Phosphate (0.8–1.4) mmol/l</th>
<th>Albumin (35–55) g/l</th>
<th>Creatine kinase (25–200) iu/l</th>
<th>Lactate dehydrogenase (350–700) iu/l</th>
<th>Thyroxine (60–160) nmol/l</th>
<th>Thyroid stimulating hormone (0.3–5.0) µu/l</th>
<th>Amylase (30–110) iu/l</th>
<th>Haemoglobin (M13.5–18) (F11.5–16.5) g/dl</th>
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</thead>
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<tr>
<td>1</td>
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<td>139</td>
<td>4.4</td>
<td>5.2</td>
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<td>347</td>
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<td>53</td>
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<tr>
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<td>3.6</td>
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<td>84</td>
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<td>137</td>
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<td>1.8</td>
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<td>107</td>
<td>11</td>
<td>42</td>
<td>12.1</td>
</tr>
</tbody>
</table>

### Figure 4
Variation of ionised magnesium with pH. Concurrent temperature <32°C: \( iMg = -1.923 \times pH + 14.68 \) (\( n=11, r=0.583, p=0.0598 \)). Concurrent temperature >32°C: \( iMg = -0.498 \times pH + 4.264 \) (\( n=21, r=0.288, p=0.2414 \)).

**t-Test regression coefficients, t=1.549, df=28, p=0.1326 (the two slopes are not significantly different).**

### Figure 5
Variation of PTH and IL6 with ionised calcium. Presentation temperature <32°C: \( PTH = 19.57 \times iCa - 14.77 \) (\( n=13, r=0.729, p=0.0046 \)). Presentation temperature >32°C: \( PTH = -29.42 \times iCa + 39.48 \) (\( n=14, r=0.713, p=0.0042 \)).

**t-Test regression coefficients, t=4.578, df=23, p=0.0002 (the two slopes are significantly different).**

**Presentation temperature <32°C: IL6 = 633.0 \times iCa - 682.2 \) (\( n=13, r=0.775, p=0.0019 \)). Presentation temperature >32°C: IL6 = -1233 \times iCa + 1479 \) (\( n=14, r=0.706, p=0.0039 \)).**

**t-Test regression coefficients, t=4.678, df=23, p<0.0001 (the two slopes are significantly different).**
kinase concentrations on admission and two patients had increased amylase levels (see table 2 for baseline biochemistry).

Figure 2 shows that rewarming to 32°C had no significant effect on the presenting acidosis (p=0.1740); above 32°C pH increased with temperature (p<0.0001). Arterial blood gas analysis showed all patients exhibited a metabolic acidosis at presentation.

Figures 3 and 4 show a negative correlation between pH and Ca\(^2+\) (p=0.0005) and Mg\(^{2+}\) (p=0.0488) below 32°C, above this temperature the relation was significant only for Ca\(^2+\) (p=0.0494). Overall there was a reduction in Ca\(^2+\) and Mg\(^{2+}\) with increasing pH.

PTH and ionised calcium correlated positively (p=0.0041) and negatively (p=0.0039) in moderate and mild hypothermia respectively (fig 5). IL6 and Ca\(^2+\) also correlated positively (p=0.0039) and negatively (p=0.0018) when presentation temperature was below and above 32°C respectively (fig 5). IL6 and PTH correlated positively (p=0.0001) (fig 6). IL1 and TNF\(\alpha\) did not correlate with Ca\(^2+\), although TNF\(\alpha\) did correlate negatively with increasing temperature (p=0.0008) (fig 7).

**DISCUSSION**

The underlying metabolic and inflammatory mechanisms associated with poor outcome in accidental hypothermia are poorly understood. It has been suggested that too rapid rewarming produces “reperfusion” type injuries,\(^7\) while deliberate hypothermia may have a protective effect on hypoxic tissues,\(^6\) suggesting that there may be an optimal rewarming strategy balancing these two effects.

This study concurs with previous observations illustrating the high mortality associated with accidental hypothermia.\(^2\) Patients who presented with moderate hypothermia (temperatures <32°C), coincident with age 84 years or over, died. Previous studies have shown that the elderly cope poorly with rapid rewarming, leading to the suggestion that slow spontaneous rewarming may be tolerated better.\(^7\)\(^8\)

Below 32°C increasing core temperature had little effect on the presenting acidosis. Rewarming above this temperature resulted in a progressive normalisation of pH. Previous studies have described the acidosis associated with hypothermia and its alleviation with temperature recovery,\(^7\) but the failure of pH to respond to increasing temperature below 32°C shown in this study has not been previously described.

It is not known whether the failure of pH to respond to temperature rise below 32°C is related to rewarming rate, or has any detrimental effect on outcome. Treatment of acidosis in hypothermia remains controversial, though induction of a respiratory alkalosis has been advocated for patients with accidental hypothermia.\(^7\)\(^11\)

Despite the presenting acidosis there was no significant change in serum potassium during the 24 hour study period, consistent with previous observations of patients with mild or moderate hypothermia.\(^5\) Increase in serum potassium as a consequence of cell injury has been shown to be prevented by hypothermia.\(^2\)\(^5\)

The fall in Ca\(^2+\) during rewarming has been described previously\(^5\) and mirrors the changes in Ca\(^^{2+}\) found in other models of tissue trauma.\(^2\)\(^5\) This fall has been shown to be pH dependent in this study; ionised magnesium and pH show a similar, but less pronounced relation. Changes in Mg\(^{2+}\) occurring during rewarming have not been previously described, though Mg\(^^{2+}\) has been shown to fall during recovery from hypothermic cardiopulmonary by pass surgery.\(^5\)

Presentation temperature seems to have a profound effect on the relation between PTH and Ca\(^{2+}\). Patients with admission temperature below 32°C, all aged 84 or over, seemed to have a non-physiological relation between PTH and Ca\(^{2+}\), high PTH concurrent with high Ca\(^^{2+}\). The mechanism underlying this is unclear but high PTH has been postulated to
be an indicator of poor outcome in patients with severe illness. Patients with admission temperatures above 32°C showed normal Ca²⁺/PTH response. A second study has shown that IL6 and PTH are increased in the presence of increased Ca²⁺ after surgery, in patients who were cooled to 30–34°C during coronary artery bypass. In our study patients rewarmed through 32°C also had increased IL6/PTH in the presence of increased Ca²⁺.

Hypothermia is associated with white blood cell activation, increased levels of cytokines and the systemic inflammatory response syndrome (SIRS). Induced hypothermia is associated with increases in mediators of SIRS in laboratory studies, and there is evidence to suggest that IL1, IL6 and TNFα may have a regulatory role in hypothermia secondary to sepsis. Different phases of hypothermia seem to be associated with different cytokines, although this is the first study to show a decrease in proinflammatory cytokines occurring during patient rewarming in a clinical setting. It is not known whether falling cytokine concentrations are beneficial, but persistently increased IL6 is associated with poor outcome.

All patients responded to rewarming but there was no normalisation of the presenting acidosis until 32°C was exceeded. During pH normalisation the fall in Ca²⁺ and Mg²⁺ was more pronounced when the temperature was below 32°C. Although data above and below 32°C have been compared separately, it should be appreciated that this division may represent different extremes of a continuum. The reversal of the expected physiological relation between PTH and ionised Ca²⁺ in those with poor outcome, who also formed the older half of our sample, was unexpected. Although the findings reported here are statistically significant, they are based on small sample sizes. The average accident and emergency department would require larger sample sizes. The average accident and emergency department would have a different cytokine profile to the ICU section. The reversal of the expected physiological relation between PTH and ionised Ca²⁺ in those with poor outcome, who also formed the older half of our sample, was unexpected. Although the findings reported here are statistically significant, they are based on small sample sizes. The average accident and emergency department would expect to see only a small number of these cases in any given year; larger sample sizes will be required to determine the relative effects of degree of hypothermia and age on both physiology and outcome.

Contributors
Mr P A Evans had the original idea, was involved in the literature search, study design, collection of data, analysis of data, editing the paper and acts as guarantor of the study. Mr J J McInerney was involved in the study design, literature search, data collection, analysis, and was principal author of the finished paper. Dr A Brekelk was involved in study design, data collection, and helped edit the paper. Dr T G Davies was involved in study design, undertook the statistical analysis and helped edit the paper. Dr W Madira was involved in study design, data collection, data analysis and edited the paper.

ACKNOWLEDGEMENTS

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