INTRODUCTION

Pyrexia occurs commonly in the first few days after acute ischemic stroke and is associated with severe stroke, large infarcts, neurologic deterioration, and poor functional outcome. It is unclear whether pyrexia is associated with poor functional outcome through its association with severe stroke (i.e., simply because pyrexia is a consequence of severe stroke) or if pyrexia accelerates ischemic brain damage and hence worsens functional outcome independently, or both. There is little information on brain temperature after ischemic stroke in patients or how temperature in the ischemic or normal brain relates to pyrexia. Nonetheless, there is increasing interest in the potential of hyperthermia to accelerate ischemic brain damage and improve stroke outcome.

Brain temperature is difficult to measure. Invasive probes only sample a restricted local volume of tissue so cannot assess temperature distribution between abnormal and normal tissue, is only possible in patients with severe stroke who justify invasive monitoring, and opening the skull may itself alter temperature dynamics. Brain temperature can be measured noninvasively using magnetic resonance (MR) spectroscopy of the hydrogen atom ($^1$H MR spectroscopy (MRS)) which, when combined with spectroscopic MR imaging (MRI), provides data on temperature distribution across the brain, including the ischemic and normal tissue, with sufficient reliability for group comparisons.

Using $^1$HMRS and diffusion-weighted imaging (DWI), we found previously in 40 patients with acute ischemic stroke that temperature in the DWI-defined ischemic tissue was elevated, particularly in the potential penumbral tissue, within 24 hours of stroke. However, we found no clear association between early temperature elevation in ischemic brain and stroke severity, although ischemic lesion temperature was higher in larger lesions. We only had body temperature measured at the time of MRI: at that time point, brain temperature was higher than body temperature, and only one of the 40 patients was pyrexial within 24 hours of admission.

The few other studies of brain temperature in acute stroke in patients used invasive brain temperature probes inserted at craniotomy; these studies found higher brain lesion than tympanic temperature, consistent with our findings using MRS, but were only able to include small numbers of patients who all had severe stroke and were unable to sample a wide range of brain tissues. No other data on temperature in normal and abnormal brain soon after ischemic stroke or at later times have been published since our original observations.

Our previous study lacked detailed information on body temperature so was unable to provide reliable information on associations with temperature in ischemic or normal brain or with outcome. We recently reported detailed body temperature...
measurements in a new cohort of 44 patients up to 7 days after stroke, showing that it was peak rather than admission measurements in a new cohort of 44 patients up to 7 days after stroke, showing that it was peak rather than admission measurements in a new cohort of 44 patients up to 7 days after stroke, showing that it was peak rather than admission measurements in a new cohort of 44 patients up to 7 days after stroke, showing that it was peak rather than admission measurements in a new cohort of 44 patients up to 7 days after stroke, showing that it was peak rather than admission measurements in a new cohort of 44 patients up to 7 days after stroke, showing that it was peak rather than admission measurements in a new cohort of 44 patients up to 7 days after stroke, showing that it was peak rather than admission.
RESULTS

We initiated recruitment on 48 patients but 2 with an intracerebral hemorrhage, 1 with complex migraine and 1 with functional limb weakness were excluded, leaving 44 patients with ischemic stroke. Four patients were unable to tolerate the admission MRI and produced no images, leaving 40 patients with initial imaging and body temperature data for analysis. No patients received licensed alteplase treatment (within 3 hours of stroke at that time); three patients were randomized to the control group in a trial of alteplase within 6 hours of ischemic stroke. The mean age was 72 years, range 37 to 88, including 19 males and 21 females. There were 12 total anterior circulation, 17 partial anterior circulation, 5 posterior circulation, and 6 lacunar syndromes on the Oxfordshire Community Stroke Project classification. The mean NIHSS on admission was 10, median 7, range 1 to 28. The median DTI ischemic lesion volume was 15.3 mL (min 0.6, max 489 mL) at baseline and 23.3 mL (min 1.4, max 621 mL) on follow-up scanning at median 5 days after stroke. At 3 months, 17 patients were alive and independent (mRS 0-2) and 23 patients were dependent or dead (mRS 3-6).

Body Temperature Profiles

All patients were normothermic on admission, the median admission tympanic temperature being 36.4 °C (min 36.0 °C, max 36.7 °C) measured at median 4.5 hours (min 1, max 19 hours) after stroke. The median peak tympanic temperature was 37.3 °C (SD 0.55; min 36.0 °C, max 38.4 °C) and was recorded at median 36 hours (1.5 days) after stroke (min 2, max 110 hours).11 Twelve patients became pyrexial during the recording period, at a median time of 29 hours (1.2 days, range 9 to 71 hours) after stroke (details provided in Karaszewski et al.1)). Patients who became pyrexial had more severe stroke on admission (NIHSS 12 versus nonpyrexial 6.5, P = 0.04), a larger DWI lesion volume on admission (58.8 versus apyrexial 6.5 mL, P = 0.008) and reached a higher peak body temperature (38.8 °C versus apyrexial 36.8 °C, P < 0.001) than patients who remained apyrexial, but there was no difference in age (71.9 versus 71.9) or time to peak temperature (40.2 versus apyrexial 49.8 hours, Table 1). Note that in some patients, the admission temperature was also the peak temperature or the peak temperature occurred soon after admission.

Table 1. Characteristics of patients who became pyrexial and who remained apyrexial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No pyrexia (n = 28)</th>
<th>Pyrexia (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.9 (11.7)</td>
<td>71.9 (11.3)</td>
</tr>
<tr>
<td>P</td>
<td>0.990</td>
<td></td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission NIHSS (median, IQR)</td>
<td>6.5 (3–10)</td>
<td>12 (5–18)</td>
</tr>
<tr>
<td>DWI lesion volume (median)</td>
<td>6,521</td>
<td>58,052</td>
</tr>
<tr>
<td>P</td>
<td>0.038</td>
<td>0.008</td>
</tr>
<tr>
<td>Body temperature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak (mean °C, SD)</td>
<td>36.8 (0.4)</td>
<td>37.8 (0.3)</td>
</tr>
<tr>
<td>Time to peak (mean hours after onset, SD)</td>
<td>49.8 (24.5)</td>
<td>40.2 (25.3)</td>
</tr>
<tr>
<td>P</td>
<td>0.990</td>
<td>0.262</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS ≤ 2</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>mRS ≥ 3</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>P</td>
<td>0.061</td>
<td></td>
</tr>
</tbody>
</table>

DWI, diffusion-weighted imaging; IQR, interquartile range; mRS, modified Rankin Scale; MWU, Mann–Whitney U-test; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation. Pyrexia was any body (aural) temperature measurement ≥ 37.5 °C during the recording period.

Statistical Analysis

All statistical comparisons were performed with nonparametric tests unless there were 20 or more observations and the variances were equal (variances were compared using Leven’s test). We compared temperatures between five brain tissue subregions (DAL, PAL, PAL +, INL, and CNL) and between brain regions and body temperature using Kruskal–Wallis and Mann-Whitney U-tests. The correlation between temperatures of brain tissue subregions and NIHSS at admission was tested with the Spearman method.

was measured by a trained observer manually outlining the hyperintense tissue on each slice on which it was visible in Analyze (Mayo Clinic, Rochester, MN, USA).

Figure 1. Example of voxel grid categorization according to tissue appearance on diffusion tensor imaging (DTI). CNL, contralateral normal brain; DAL, definitely abnormal tissue; INL, ipsilateral normal brain; PAL, possible abnormal tissue; PAL +, tissue one voxel thick immediately outside the lesion.
Brain Temperatures

The median time from stroke onset to admission MRI was 17 hours (range 3 to 26 hours): nine patients were imaged <6, three between 6 and 12, 14 between 12 and 18 hours, and 14 between 18 and 26 hours after stroke. Data available for some of the analyses of brain temperature were further reduced due to impaired spectra (patient movement or poor shimming) or no follow-up imaging (early patient discharge or too ill/died), but all available data were used in each analysis. Therefore, brain temperature data were available for a total of 35 patients at each time point of whom 30 individual patients provided brain temperature measures at both time points and 10 provided brain temperature measures at one or other time point but not both.

At the time of the admission MRI, the median temperatures of lesion core (DAL, 38.6°C) and potential penumbra (PAL, 38.3°C; PAL+, 38.7°C) were higher than temperatures of INL (37.6°C) and CNL brain (37.9°C: abnormal versus normal tissues, P = 0.03; CNL versus INL, P < 0.05; Figure 2). Thirty-seven patients underwent follow-up MRI, performed at median 5 days (range 3 to 7 days) after stroke, of whom 35 contributed brain temperature data. The temperature in DAL (38.8°C), PAL (38.1°C), and PAL+ (38.1°C) tissue and in DWI-normal tissues (ipsilateral 38.4°C, contralateral 38.5°C) were all similar (P = 0.3; Figure 2).

Brain and Body Temperature Comparison

On admission MRI, all brain regions, whether DWI-abnormal or normal appearing, were hotter than concurrently measured tympanic temperatures (mean 36.6°C, P < 0.001, 0.032 and 0.001, respectively) (Figure 3A). On follow-up MRI, all brain regional temperatures remained hotter than tympanic temperature measured concurrently (mean 36.3°C, P < 0.001 all comparisons, Figure 3B).

On admission MRI, the temperature in the INL or CNL-appearing brain did not differ in the 12 patients who became pyrexial from that in 28 who remained apyrexial, either on the baseline (ipsilateral, pyrexial 37.6°C versus apyrexial 37.4°C, P = 0.9; contralateral, pyrexial 37.3°C versus apyrexial 37.8°C, P = 0.4) or the follow-up scan (ipsilateral, pyrexial 38.4°C versus apyrexial 38.4°C, P = 0.9; contralateral, pyrexial 38.8°C versus apyrexial 38.4°C, P = 0.5), Figure 4.

Admission brain temperature, early and late imaging, and clinical outcomes

Between admission and follow-up imaging, 11 patients showed lesion expansion and 27 patients had either no change or a reduction in DWI lesion size (2 patients did not have a follow-up scan). Mean temperature of CNL tissue on admission was higher in patients whose lesion grew (38.3°C) than in those whose lesion did not expand (37.7°C, P = 0.014) at follow-up. There was no

Figure 2. Temperatures (mean of patients’ means shown) (°C) of ischemic and normal-appearing brain at admission to hospital and follow-up at around 5 days after stroke. CNL, contralateral normal brain; CSI, chemical shift imaging; DAL, definitely abnormal tissue; INL, ipsilateral normal brain; PAL, possible abnormal tissue; PAL+, tissue one voxel thick immediately outside the lesion.

Figure 3. Brain and body temperature (A) on admission and (B) at median 5 days after stroke. CI, confidence interval.

Figure 4. Tympanic temperature and temperature in ipsilateral and contralateral normal-appearing brain tissue in patients who became pyrexial at any time within the first 7 days after admission and those who did not. CI, confidence interval.
between ischemic brain temperature and admission stroke severity. The associations between CNL temperature and clinical findings parallel those found for tympanic temperature in the same patients\textsuperscript{11} and that others have found for body temperature in other studies\textsuperscript{2-10} summarized in Karaszewski et al.\textsuperscript{11} The difference in the pattern of brain temperature elevation in the ischemic lesion, combined with the different associations with clinical and imaging features, suggests that the mechanism(s) for early temperature elevation in ischemic brain are different to those which elevate temperature in normal-appearing brain and cause pyrexia. This leads to several important conclusions:

(a) The elevated temperature in ischemic tissue is not directly related to body temperature and possibly not to progression of brain injury, and appears to have a different mechanism to that of body and normal-appearing brain temperature;

(b) that body temperature elevation after ischemic stroke occurs secondary to the systemic (presumably inflammatory) response to brain injury and is reflected in temperature in normal-appearing brain. Hence, body temperature takes time to rise, peaks at around 1 to 2 days after stroke onset, and (as summarized previously\textsuperscript{11}) patients are usually apyrexial within the first few hours of stroke. None of the present study patients was pyrexial on admission; 12 became pyrexial up to 5 days after stroke. This interpretation is also consistent with the observed relationship between plasma inflammatory markers and temperature profiles in normal-appearing but not in ischemic brain, reported previously\textsuperscript{30};

(c) and that brain temperature is consistently higher than body temperature, perhaps due to the heat byproducts of the metabolically very active brain.

The early temperature elevation in ischemic brain has several explanations. It may reflect continued cell metabolism generating heat but inadequate blood flow to remove the heat and cool the tissue, or activation of mechanisms intended to counteract ischemic damage by dissipating energy, that cannot be used by ischemic cells, as heat. For example, genes that control mitochondrial oxidative activity like uncoupling proteins mediate tolerance to ischemic insults in experimental models\textsuperscript{31} and uncoupling proteins single-nucleotide polymorphisms are associated with risk of cardiovascular disease in humans.\textsuperscript{32}

This study has limitations. The relatively small sample size (40) reflects the difficulty in undertaking complex MRI studies in patients with moderate to severe acute stroke. The absence of other studies of brain temperature after stroke and the very few using spectroscopy is testament to this difficulty. Nonetheless, we have doubled the existing literature: data on 80 patients in two independent studies show the same brain temperature pattern after ischemic stroke. In both current and previous studies,\textsuperscript{17,18} temperatures across the brain were measured at a relatively wide range of times (baseline up to 26 hours after stroke), many within the first 12 hours. However, within the first 24 hours, many pathologic processes occur in ischemic brain\textsuperscript{33,34} that are likely to influence local heat production and dissipation. However, the comparison of ischemic with nonischemic brain and body temperature is valid as each patient acted as their own control. None of the patients received alteplase: therefore, these results reflect the ‘natural history’ of nonthrombolysis-treated ischemic stroke. It is possible that alteplase, by restoring tissue perfusion, will alter ischemic tissue temperature profiles, or by reducing stroke severity and infarct extent will alter body temperature profiles and reduce pyrexia. The work should be repeated in thrombolysis-treated patients. We only performed limited multivariate statistical modeling as the sample size precluded reliable results.

Methodological limitations related to \textsuperscript{1}H MR thermometry, discussed previously,\textsuperscript{15,17,18} are worth reiterating. Calibration, in

<table>
<thead>
<tr>
<th>Table 2. Comparison between brain temperature (°C) on admission and ischemic lesion expansion by median 5 days after stroke, change in NIHSS from admission to 5 days after stroke, and functional outcome at 3 months</th>
<th>Admission brain temperatures (°C)</th>
<th>DAL</th>
<th>PAL</th>
<th>PAL +</th>
<th>INL</th>
<th>CNL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic lesion expansion by 3–5 days</td>
<td>Lesion expansion</td>
<td>38.8 (3)</td>
<td>37.9 (7)</td>
<td>38.0 (3)</td>
<td>37.1 (6)</td>
<td>38.3 (10)</td>
</tr>
<tr>
<td>No lesion expansion</td>
<td>38.7 (8)</td>
<td>38.0 (16)</td>
<td>38.8 (13)</td>
<td>37.7 (21)</td>
<td>37.7 (23)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.54</td>
<td>0.32</td>
<td>0.45</td>
<td>0.13</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Change in NIHSS from admission to 120 hours after stroke</td>
<td>No improvement in NIHSS</td>
<td>39.3 (6)</td>
<td>38.8 (11)</td>
<td>38.4 (9)</td>
<td>38.0 (15)</td>
<td>38.1 (18)</td>
</tr>
<tr>
<td>Improvement in NIHSS</td>
<td>37.7 (4)</td>
<td>37.5 (12)</td>
<td>39.1 (8)</td>
<td>37.3 (13)</td>
<td>37.9 (15)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td>0.04</td>
<td>0.37</td>
<td>0.04</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Functional outcome at 3 months</td>
<td>Poor outcome mRS 3-6</td>
<td>38.7 (10)</td>
<td>38.6 (13)</td>
<td>38.9 (8)</td>
<td>37.6 (13)</td>
<td>38.2 (19)</td>
</tr>
<tr>
<td>Good outcome mRS 0-2</td>
<td>38.8 (1)</td>
<td>37.7 (11)</td>
<td>38.6 (9)</td>
<td>37.6 (16)</td>
<td>37.6 (16)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.91</td>
<td>0.31</td>
<td>0.96</td>
<td>0.59</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

CNL, contralateral normal brain; DAL, definitely abnormal tissue; INL, ipsilateral normal brain; PAL, possible abnormal tissue; PAL +, tissue one voxel thick immediately outside the lesion; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale. Number in brackets is number of patients in each category. Temperatures are °C. Bold values highlight differences that are significant.
this and our previous work, currently assumes that brain temperature in healthy subjects is 37°C. However, some data suggest that normal brain temperature may be slightly higher; in volunteer studies, we find temperatures of 38°C even with this calibration (unpublished data). Unfortunately, there is no reference standard. True temperatures may be slightly different to the values given by 1HMRS thermometry, but within an individual they are comparable. More studies are required to examine important factors like temperature variation in gray and white matter, effect of tissue water content, and stage in infarction.

This study has strengths. MR thermometry enables simultaneous measurement of tissues across the ischemic lesion to normal brain. Other studies have measured brain temperatures using invasive probes, but this restricts measurement to a small volume of brain, of uncertain location, affects brain temperature through breaching the skull and can only be used when invasive monitoring is justified clinically, i.e., in the severe strokes. We performed all assessments in standardized ways, blinded all analyses. We used operational definitions of ischemic lesion core and potential penumbral tissues.18 We used validated software to assign tissue classifications, with good rater reliability and biologic relevance.27 Our sample, though small, was representative of hospital admit patients.

Why should body temperature be related to initial stroke severity, and why should body temperature elevation adversely influence lesion growth and functional outcome? Experimental data suggest that higher temperatures not only accelerate ischemic damage but also accelerate opening of the blood–brain barrier.35 If these observations also apply in humans,35 then higher temperatures in contralateral brain could influence lesion progression and worsen outcome by promoting blood–brain barrier opening in the ischemic tissue, exacerbating tissue swelling, worsening tissue capillary blood flow, leading to recruitment of more tissue into the ischemic lesion, lesion expansion and worse functional outcome.35

If the foregoing interpretation is correct, then therapeutic hypothermia might work by cooling nonischemic tissue, preventing blood–brain barrier opening, reducing peri-infarct damage, and preventing infarct growth, but might not have much influence on the primary ischemic core tissue. Hence, the combination of thrombolysis to salvage ischemic but viable cells,37 plus hypothermia to reduce blood–brain barrier opening, tissue edema, and recruitment of peri-infarct tissue into the infarct, might be doubly effective in improving functional outcome. Thrombolysis might also enhance hypothermia because the act of restoring blood flow to the ischemic cells could also help to remove the excess heat generated. Thus, therapeutic hypothermia might be beneficial even if started >6 hours after stroke and even modest reductions of only 1°C or 2°C might protect at risk tissue from progression to permanent damage or recruitment of initially not at risk tissue into the infarct. Further trials of hypothermia38 should be encouraged to test these hypotheses. If our observations are correct, then body temperature is likely to be the more relevant measure for clinical outcomes.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest

ACKNOWLEDGEMENTS

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REFERENCES


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