ORIGINAL RESEARCH

Persistent middle cerebral artery occlusion associated with lower body temperature on admission

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Background: Low body temperature is considered neuroprotective in ischemic stroke, yet some studies suggest that low body temperature may also inhibit clot lysis and recanalization. We hypothesized that low body temperature was associated with persistent proximal middle cerebral artery (MCA) occlusion in patients with acute ischemic stroke presenting with symptoms of proximal MCA occlusion, suggesting a possible detrimental effect of low body temperature on recanalization.

Methods: All patients with acute ischemic stroke admitted to our Stroke Unit between February 2006 and August 2012 were prospectively registered in a database. Computed tomography (CT) angiography was performed in patients admitted <6 hours after stroke onset. Based on presenting symptoms, patients were classified according to the Oxford Community Stroke Project classification (OCSP). Patients with symptomatic proximal MCA occlusion were compared to patients with total anterior circulation infarct (TACI) without MCA occlusion on CT angiography.

Results: During the study period, 384 patients with acute ischemic stroke were examined with CT angiography. A total of 79 patients had proximal MCA occlusion and 31 patients had TACI without MCA occlusion. Median admission body temperatures were lower in patients with MCA occlusion compared to patients without occlusion (36.3°C versus 36.7°C, $P = 0.027$). Admission body temperature <36.5°C was independently associated with persistent MCA occlusion when adjusted for confounders in multivariate analyses (odds ratio 3.7, $P = 0.007$).

Conclusion: Our study showed that low body temperature on admission was associated with persistent proximal MCA occlusion. These results may support a possible detrimental effect of low body temperature on clot lysis and recanalization.

Keywords: body temperature, clot lysis, ischemic stroke, MCA occlusion

Introduction

Body temperature is an important topic in ischemic stroke. As hypothermia is considered a robust neuroprotectant and has shown efficiency against a variety of brain injuries at an experimental level, the influence of body temperature and hypothermia on ischemic stroke is of great interest.[1] However, the impact of body temperature on clot lysis in the acute phase of ischemic stroke is unclear. Observation studies in stroke patients have shown an association between increased body temperature within the first 12–24 hours of stroke onset and poor prognosis.[2–4] On the other hand, a meta-analysis of clinical randomized trials could not find evidence to support the use of either pharmacological or physical strategies to reduce body temperatures in the acute phase of ischemic stroke.[5] Some studies have suggested a possible relationship between

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297

body temperature and clot lysis, as lower temperatures may lead to a decreased rate of clot lysis and thus delayed recanalization.[6–8] We recently reported that stroke patients treated with tissue plasminogen activator (tPA) presenting with higher body temperatures were more likely to achieve favorable outcomes compared to patients presenting with lower body temperatures, suggesting improved clot lysis at higher temperatures.[9] Another recently published study showed an increased benefit of tPA in patients with ischemic stroke and increased body temperature.[10]

In ischemic stroke, the middle cerebral artery (MCA) is frequently occluded.[11] However, a number of ischemic stroke patients presenting with clinical proximal MCA occlusion have normal computed tomography (CT) angiograms on admission, which may be explained by early recanalization. We hypothesized that low admission body temperature was associated with persistent proximal MCA occlusion in patients with acute ischemic stroke presenting with acute symptoms of MCA occlusion, suggesting a possible detrimental effect of low body temperature on clot lysis and early recanalization.

Methods

All consecutive patients with acute cerebral infarction admitted to the Stroke Unit, Department of Neurology, Haukeland University Hospital in Bergen between February 2006 and August 2012 were prospectively registered in a database (The Bergen NORSTROKE Registry). Cerebral infarction was defined in accordance with the Baltimore–Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting longer than 24 hours because of ischemic lesions or transient ischemic attacks where CT or magnetic resonance imaging (MRI) showed infarctions related to the clinical findings.[12]

CT angiography was performed on admission in patients where the treating neurologist suspected symptom debut less than 6 hours prior to hospital admission unless specific contraindications to iodinated contrast agents were present (including history of contrast agent allergy, pregnancy, and renal insufficiency). Degree of internal carotid stenosis was evaluated with duplex ultrasound examination within 24 hours after admission.

Based on presenting symptoms, patients were classified according to the Oxford Community Stroke Project classification (OCSP).[13]

Patients were assigned to a first group (occlusion group) if they had ischemic stroke with symptom debut <6 hours due to acute proximal MCA occlusion present on admission CT angiography. Patients with ischemic stroke with symptom debut <6 hours were assigned to a second group (no-occlusion group) if they presented with total anterior circulation infarct (TACI) without MCA occlusion on admission CT angiography and without internal carotid artery occlusion or 50%–99% stenosis on duplex ultrasound. Patients with internal carotid stenosis of 50%–99% were excluded from the no-occlusion group because significant internal carotid stenosis may cause cerebral infarction and TACI without embolism due to hypoperfusion.[14,15]

Body temperature was obtained on admission in addition to blood pressure and blood tests. Body temperature was measured by either an infrared tympanic device (LightTouch-LTX; Exergen Corp, Watertown, MA, USA) or by using a temporal artery thermometer (Exergen Temporal Scanner; Exergen Corp). The precision of both methods has been validated in several trials.[16–19] Prior to temperature measurement, no temperature intervention (paracetamol or intravenous administration of fluids) was provided. The National Institute of Health Stroke Scale (NIHSS) was used to assess stroke severity on admission. The study was approved by the local research ethics committee.

Neuroimaging

Nonenhanced CT and CT angiographic sequences were performed according to a standard departmental stroke protocol with an 8- or 16-section multidetector CT scanner (LightSpeed; GE Healthcare Bio-Sciences Corp, Piscataway, NJ, USA). Representative sample parameters were as follows: 120 kVp, 300 mA, 2 second scan time and 5 mm section thickness. Nonenhanced CT was immediately followed by CT angiography. Scan delay time was determined by using SmartPrep and 80 mL of a nonionic contrast agent (Iomeron; Bracco Imaging, Milano, Italy) was administered at an injection rate of 2.0 mL/second through an 18-gauge intravenous catheter by using a power injector (Medrad Stellant; Medrad, Warrendale, PA, USA). The following parameters were used: 100 kVp, 300 mA, 2.5 mm section thickness, 1.25 mm reconstruction interval, and 1.35:1 pitch. Images were obtained from the level of the C5 vertebral body through the skull. Nonenhanced CT scans and CT angiography scans were reviewed by a stroke neurologist and stroke neurologist research fellow experienced in neuroimaging review (Halvor Naess and Christopher Kvistad, 15 and 4 years of neuroimaging experience, respectively). An interrater agreement was evaluated on 20 random patients as to presence of proximal MCA occlusions or not. Reviewers had information regarding

age, sex, and clinical symptoms of the patients but were blinded to clinical outcome.

Statistics

Univariate analyses were performed comparing patients in the occlusion group with patients in the no-occlusion group. We stratified for admission body temperature ($<36.5°C$ versus $\geq36.5°C$). A second univariate analysis was performed comparing patients with admission body temperatures above and below $36.5°C$. Student's t-test and ANOVA were used to compare mean values and the Wilcoxon rank sum test was used to compare median values. A logistic regression analysis was performed by backward elimination with the presence of proximal MCA occlusion or not as the dependent variable. Analyses were performed using STATA 11.0 (StataCorp LP, College Station, TX, USA).

Results

Interrater agreement on presence of proximal MCA occlusions diagnosed with CT angiography was good (weighted $\kappa = 0.93$, $P < 0.001$). During the study period, 384 patients with acute ischemic stroke were examined with CT angiography, of which 79 patients had acute proximal MCA occlusion and were included in the occlusion group. A total of 51 patients had TACI without MCA occlusion, of which 16 patients were excluded due to internal carotid artery occlusion and four patients were excluded due to significant internal carotid artery stenosis. In total, 31 patients had TACI without MCA occlusion or internal carotid artery occlusion or significant internal carotid artery stenosis and were included in the no-occlusion group. Of the 79 included patients in the occlusion group, 20 patients (33.0%) had concomitant internal carotid artery occlusion and eight patients (10.1%) had concomitant 50%–99% internal carotid stenosis. Table 1 shows demographic data of patients in the two groups. Mean age was 70.9 years in the occlusion group and 75.8 years in the no-occlusion group ($P = 0.067$) and there were 46 males (58.2%) in the occlusion group compared to 15 males (48.4%) in the no-occlusion group ($P = 0.350$). Fewer patients in the occlusion group had experienced previous transient ischemic attack (TIA) as compared to the no-occlusion group (four [5.0%] versus seven [22.6%], respectively, $P = 0.006$). Median NIHSS scores on admission were similar in both groups ($P = 0.400$) and median systolic

Table 1 Univariate analysis of demographic data and clinical characteristics in patients with proximal MCA occlusion versus patients with clinical MCA occlusion without occlusion on admission

	Proximal MCA occlusion (n = 79)	Clinical MCA occlusion without occlusion (n = 31)	P-value
Age, years, mean (SD)	70.9 (15.3)	75.8 (15.0)	0.067
Male sex (%)	46 (58.2)	15 (48.4)	0.350
Time from ictus to admission in hospital, minutes, median (IQR)	90.0 (61.9–149.1)	95.6 (61.9–115.3)	0.897
Prior diseases (%)			
Ischemic stroke	5 (6.3)	3 (9.7)	0.543
TIA	4 (5.0)	7 (22.6)	0.006
Myocardial infarction	20 (25.3)	4 (12.9)	0.156
Diabetes mellitus	13 (16.7)	9 (29.0)	0.147
Hypertension	43 (54.4)	15 (48.4)	0.568
Atrial fibrillation	31 (39.2)	16 (51.6)	0.238
Status on admission			
NIHSS score, median (IQR)	18 (13–22)	16 (12–20)	0.400
Body temperature, median (IQR)	36.3 (36.0–36.8)	36.7 (36.4–37.0)	0.027
Body temperature $<36.5°C$ (%)	46 (58.2)	10 (32.3)	0.014
Systolic blood pressure, mmHg, median (IQR)	150 (139–173)	161 (145–186)	0.026
Diastolic blood pressure, mmHg, median (IQR)	76 (64–92)	86 (73–94)	0.060
Blood tests on admission			
Hemoglobin, g/dL, median (IQR)	14.2 (13.2–15.3)	13.5 (12.5–15.2)	0.181
Leucocytes, 10*9/L, median (IQR)	8.6 (7.2–10.9)	8.1 (7.2–10.5)	0.745
Glucose, mmol/L, median (IQR)	6.5 (5.7–7.9)	7.1 (6.2–8.4)	0.060
C-reactive protein, mg/L, median (IQR)	3 (1–6)	4 (2–15)	0.128
D-dimer, mg/L, median (IQR)	1.0 (0.5–1.6)	1.5 (0.5–2.7)	0.337
Fibrinogen, g/L, median (IQR)	3.4 (3.0–4.0)	3.6 (3.2–4.1)	0.235

Abbreviations: IQR, interquartile range; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.

blood pressure was lower in the occlusion group than in the no-occlusion group (150 mmHg versus 161 mmHg, $P = 0.026$). Median body temperature on admission was 36.3°C in the occlusion group and 36.7°C in the no-occlusion group ($P = 0.027$). More patients in the occlusion group had an admission body temperature <36.5°C as compared to the no-occlusion group (46 [58.2%] versus ten [32.3%], respectively, $P = 0.014$).

There were no baseline differences in patients with lower body temperatures (<36.5°C) compared to patients with higher body temperatures (≥36.5°C), except mean age, which was higher in patients with lower body temperatures (75.8 years versus 68.7 years, $P < 0.001$).

Table 2 shows logistic regression analyses with the presence of proximal MCA occlusion or no presence of proximal MCA occlusion as the dependent variable and age, sex, NIHSS score on admission, and admission body temperature <36.5°C as independent variables. A low admission body temperature of <36.5°C was independently associated with the presence of MCA occlusion (odds ratio 3.7, $P = 0.007$). Systolic blood pressure and prior TIA were not independently associated with persistent MCA occlusion when implemented in logistic regression analyses and did not change the significant association between low admission body temperature and persistent MCA occlusion (analysis not shown). Admission body temperature did not correlate with admission systolic blood pressure (correlation coefficient 0.05, $P = 0.617$) or prior TIA (correlation coefficient 0.11, $P = 0.273$).

Discussion

Our study showed that low body temperature on admission was associated with persistent proximal MCA occlusion. This may be explained by an inhibiting effect of low body temperature on clot lysis, preventing recanalization in patients with proximal MCA occlusions, whereas higher body temperatures may have led to an early recanalization in patients presenting with clinical proximal MCA occlusion

Table 2 Multivariate analysis with persistent proximal MCA occlusion versus no occlusion as dependent variable

	OR	95% CI	P-value
Age	0.97	0.94–1.00	0.057
Sex	0.80	0.32–2.00	0.640
NIHSS score on admission	1.03	0.96–1.11	0.394
Body temperature on admission <36.5°C	3.72	1.43–9.64	0.007

Abbreviations: CI, confidence interval; MCA, middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.

but no detectable occlusion on admission CT angiography. Another potential explanation of our findings may have been that patients with MCA occlusion had lower body temperatures on admission due to more severe neurological deficits initially and therefore less muscle activity than patients without MCA occlusion. In addition, a longer time from symptom onset to hospital admission and temperature measurement may have led to lower temperatures in patients arriving late at the hospital. However, these possibilities are unlikely, since time from ictus to admission and NIHSS scores on admission were similar in both groups.

Patients with persistent MCA occlusion had a lower rate of prior TIA as compared to patients presenting without MCA occlusion where an early recanalization may have occurred. TIA has been defined as an episode of neurological symptoms of presumed vascular etiology that resolves within 24 hours as a result of spontaneous recanalization of an occluded cerebral vessel.[20] Previous studies have shown that patients with a history of TIA prior to an ischemic stroke present with milder initial clinical symptoms and tend to have smaller infarct volumes and a higher rate of recanalization compared to patients without prior TIA, suggesting a protective effect of TIA before ischemic stroke.[21–23] In our study population, patients with prior TIA may thus have been more inclined to an early recanalization, resulting in a lower rate of prior TIA in patients with persistent MCA occlusion. Patients with persistent MCA occlusion also presented with lower systolic blood pressures than patients without MCA occlusion. This is in line with other studies which have suggested that blood pressure elevation may be needed to achieve early recanalization and minimize ischemic damage.[24,25] However, systolic blood pressure and prior TIA were not independently associated with persistent MCA occlusion in multivariate analyses and did not correlate with admission body temperature. Our results suggest that prior TIA, blood pressure, and body temperature are associated with recanalization by different mechanisms.

Our results are in conformity with the findings from in vitro studies where lower temperatures led to a decrease in fibrinolytic activity when tPA was added to clot suspensions.[7] A pooled analysis of these studies found a 5% reduction in fibrinolytic activity per degree Celsius decrease in temperature.[26] Our findings are also in line with other observational studies.[6,9,10] A recent study, which included 647 ischemic stroke patients treated with tPA, reported an association between high baseline body temperature and favorable outcome after 3 months, suggesting an increased rate of clot lysis in patients with increased body temperatures.[10]

We previously showed an association between high body temperature on admission and favorable outcome in 111 patients treated with tPA, indicating that the effect of high body temperature on clot lysis was more important than the neuroprotective effect of low body temperature in the acute phase of ischemic stroke.[9] In addition, a recent study found an association of lower admission body temperature and more severe stroke in patients with ischemic stroke, yet no such association was found in patients with acute cerebral hemorrhage.[6] A detrimental effect of low body temperature on pre-hospital clot lysis and recanalization was considered as a likely explanation. The impact of baseline body temperature on clot lysis has not been assessed in randomized trials of ischemic stroke patients or in a pooled analysis of these trials.

Treatment of elevated body temperatures with pharmacological or physical strategies has been established in patients with acute ischemic stroke, even though there are no randomized trials favoring such strategies. A randomized, placebo-controlled study including 1400 patients with ischemic stroke showed no overall effect of paracetamol on outcome.[27] In addition, a systematic review of clinical randomized trials did not support the use of pharmacological or physical strategies to reduce body temperature in patients with acute ischemic stroke.[5] Our study may explain these disappointing results to treat stroke patients with different cooling strategies. Although cooling represents a potent neuroprotective therapy, a prolonged time to spontaneous recanalization may negate this benefit in the acute phase of ischemic stroke.

There are some limitations in this study. We did not have direct data of recanalization in the patients in the no-occlusion group, although it was assumed that recanalization had occurred. However, as all patients in the no-occlusion group had ischemic stroke with severe symptoms on admission and patients with symptomatic internal carotid artery occlusion or significant stenosis were excluded, it seems likely that these patients had an initial occlusion which had recanalized prior to admission CT angiography. In addition, the number of patients in the no-occlusion group was relatively low. However, this number was extracted from CT angiography of 384 ischemic stroke patients, indicating that patients with TACI without occlusion on admission are relatively rare. A strength of this study was the prospective nature of the protocol in a single-center study.

To conclude, low body temperature on admission was associated with persistent proximal MCA occlusion. The lower body temperatures in patients with persistent MCA occlusion may have impeded recanalization. These results may support a possible detrimental effect of low body temperature on clot lysis and recanalization.

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Disclosure

The authors report no conflicts of interest in this work.

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