Induced Normothermia Attenuates Cerebral Metabolic Distress in Patients With Aneurysmal Subarachnoid Hemorrhage and Refractory Fever

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Background and Purpose—The purpose of this study was to analyze whether fever control attenuates cerebral metabolic distress after aneurysmal subarachnoid hemorrhage (SAH).

Methods—Eighteen SAH patients, who underwent intracranial pressure (ICP) and cerebral microdialysis monitoring and were treated with induced normothermia for refractory fever (body temperature ≥38.3°C, despite antipyretics), were studied. Levels of microdialysate lactate/pyruvate ratio (LPR) and episodes of cerebral metabolic crisis (LPR >40) were analyzed during fever and induced normothermia, at normal and high ICP (>20 mm Hg).

Results—Compared to fever, induced normothermia resulted in lower LPR (40 ±24 versus 32 ±9, P<0.01) and a reduced incidence of cerebral metabolic crisis (13% versus 5%, P<0.05) at normal ICP. During episodes of high ICP, induced normothermia was associated with a similar reduction of LPR, fewer episodes of cerebral metabolic crisis (37% versus 8%, P<0.01), and lower ICP (32 ±11 versus 28 ±12 mm Hg, P<0.05).

Conclusions—Fever control is associated with reduced cerebral metabolic distress in patients with SAH, irrespective of ICP. (Stroke. 2009;40:1913-1916.)

Key Words: fever ■ induced normothermia ■ cerebral microdialysis ■ lactate/pyruvate ratio ■ SAH

Fever exacerbates brain damage1 and is associated with worse outcome in patients with aneurysmal subarachnoid hemorrhage (SAH).2 However, the exact mechanisms underlying this association are not entirely clear in humans. Furthermore, although fever control is recommended in brain-injured patients,3 its clinical benefits have yet to be established. Elevated extracellular lactate/pyruvate ratio (LPR), measured in the interstitial space by cerebral microdialysis, is a marker of brain metabolic distress and is associated with poor outcome after SAH.4 In this study, we examined the effect of fever control on biochemical markers of cerebral metabolic distress in patients with SAH.

Methods

Patients

Patients were retrospectively identified from an ongoing prospective database, under Institutional Review Board approval. Consecutive SAH patients admitted to the Neuro-ICU at the Hospital of the University of Pennsylvania who underwent cerebral microdialysis and intracranial pressure (ICP) monitoring and were treated with induced normothermia for refractory fever were studied. Patients were monitored if their admission Glasgow Coma Scale (GCS) was ≤8 or they later deteriorated to this level.

Fever Control

Refractory fever was defined as a sustained fever (rectal temperature ≥38.3°C), despite antipyretics, which was treated with induced normothermia (target temperature: 37°C) with the use of ice packs and an external cooling device (Arctic Sun, Medivance Inc or Blanketrol II, Cincinnati SubZero). Patients treated with mild hypothermia were excluded.

General Management

Patients were managed with a standard protocol that included prehospital and ICU resuscitation, early aneurysm occlusion, and aggressive prevention and treatment of intracranial hypertension and vasospasm.5 ICP was kept <20 mm Hg using a stepwise management strategy (ie, cerebrospinal fluid drainage, mild hyperventilation to PaCO2 30 to 34 mm Hg, mannitol, and hypertonic saline). Symptomatic vasospasm was defined by the presence of neurological deterioration (ie, focal deficits not present on admission or deterioration in the level of consciousness) associated with angiographic vasospasm.

Intracranial Monitoring

A microdialysis catheter (CMA Microdialysis) and an ICP probe (Camino, Integra Neurosciences) were inserted at the bedside through a burr-hole and secured with a triple-lumen bolt. The probes were placed into white matter contralaterally to the hemisphere with maximal focal injury. A noncontrast head CT scan was performed on each patient to confirm accurate position of the probe in normal

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appearing white matter, distant from the injured tissue. The microdialysis catheter was perfused with sterile artificial CSF at a rate of 0.3 μmol/min. Samples were collected hourly and analyzed for glucose, lactate, and pyruvate.

Data Analysis
An elevated LPR is a marker of brain damage, and values of LPR >40 are associated with ongoing cell energy dysfunction and cerebral metabolic crisis. Mean LPR values and episodes of cerebral metabolic crisis (ie, the percentage of hourly measurements with LPR >40) were examined during fever (temperature >38.3°C) and during induced normothermia (temperature 36 to 38.2°C). Because fever is a risk factor for elevated ICP, analysis was performed separately on samples collected at normal (ICP ≤20 mm Hg) or elevated ICP (>20 mm Hg).

Statistical analysis of pooled data were performed using Student t test for continuous variables and χ² test for categorical variables. A probability value <0.05 was considered statistically significant.

Results
Patient Characteristics
A total of 1637 microdialysate samples and corresponding ICP and temperature measurements from 18 SAH patients were analyzed. Patient characteristics are depicted in Table 1.

Effect of Induced Normothermia on Cerebral Metabolic Distress
During periods of normal ICP (Figure, A), compared to fever (n=495), induced normothermia (n=998) was associated with a significant reduction of LPR 40±24 versus 32±9, P<0.01) and with fewer episodes of cerebral metabolic crisis (13% versus 5%, P<0.05). When ICP was >20 mm Hg (Figure, B), induced normothermia (n=109) was associated with lower LPR (34±36 versus 40±47, P<0.01) and ICP (28±12 versus 32±11 mm Hg, P<0.05), and with a reduced rate of cerebral metabolic crisis (8% versus 37%, P<0.01) than fever (n=35).

Attenuation of Cerebral Metabolic Distress by Induced Normothermia: Relationship With Outcome
Outcome at hospital discharge was assessed using the Glasgow Outcome Score (GOS). Patients with GOS 4 and 5 (moderate disability and full recovery) were considered to have good outcome, and those with GOS 1 to 3 (death, vegetative state, severe disability) to have poor outcome. Hunt and Hess score, Fisher grade, and the percentage of monitored time with fever did not differ significantly in patients with good outcome versus those with poor outcome. Compared to patients with good outcome, those with poor outcome had higher mean LPR (48±39 versus 33±35, P<0.01) and ICP (15±13 versus 10±7, P<0.01). In both groups, induced normothermia was associated with a significant reduction of LPR and cerebral metabolic crisis compared to fever; however, a greater reduction of elevated LPR and cerebral metabolic crisis by induced normothermia was observed in patients who eventually had poor outcome (Table 2).

Discussion
In this study, we found an association between fever and cerebral metabolic distress, suggesting a possible relationship between elevated temperature and worsened cerebral metabolic distress in SAH patients. Elevated LPR was associated with worse outcome, consistent with previous observations.4 We found that the increase of LPR by refractory fever was

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<th>Gender</th>
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<th>Fisher</th>
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ACoA indicates anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCoA, posterior communicating artery; VB, vertebro-basilar system; F, female; H&H, Hunt and Hess scale; ICHT, intracranial hypertension; M, male. Time to start of intracranial monitoring is given in days after SAH.

*Clipping; †coiling.
more pronounced in patients who eventually had poor outcome. From a clinical standpoint, this suggests that LPR might be used to identify patients at greater risk of fever-induced secondary brain damage and who may benefit most from aggressive fever control.

In animals, controlled normothermia may reduce biochemical markers of neuronal injury in vivo. In brain-injured patients, however, it has not been clearly demonstrated that normothermia attenuates brain damage, and the exact mechanisms by which this may occur are only beginning to be elucidated. Although treatment of fever is routine in neurocritical care, proof of principle and clinical benefit have yet to be demonstrated. Preliminary clinical studies have shown that mild hypothermia reduces LPR after cerebral ischemia. By showing that induced normothermia was associated with a significant reduction of elevated LPR and with fewer episodes of cerebral metabolic crisis, this study supports the notion that fever control may be neuroprotective in humans.

Fever, itself, may increase ICP. The reduction of cerebral metabolic distress after induced normothermia may therefore be partly explained by a decrease in ICP, at least during episodes of intracranial hypertension. However, because lower LPR and a reduction (albeit of less magnitude) in

**Table 2. Attenuation of Cerebral Metabolic Distress by Induced Normothermia: Relationship With Patient Outcome**

<table>
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<th>Outcome</th>
<th>Lactate/Pyruvate Ratio</th>
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<td>Fever</td>
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<td>Poor outcome (n=7)</td>
<td>67±56</td>
<td>39±21</td>
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<tr>
<td>Good outcome (n=11)</td>
<td>38±41</td>
<td>32±36</td>
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Cerebral metabolic crisis indicates No. of hourly measurements with microdialysis lactate/pyruvate ratio>40. Data are expressed as mean±SD.
cerebral metabolic crisis was observed when ICP was in the normal range, it is likely that induced normothermia exerts protective effects not only by lowering ICP, but also through other mechanisms.

This study has several limitations. First, although the data were collected prospectively, the analysis was retrospective. Second, the patient sample size was small (n = 18), but more than 1600 hourly samples were analyzed. Third, the study population was narrowly defined and included only poor grade SAH patients with refractory fever. The results cannot be generalized to patients with other or less severe forms of brain injury, and with nonsustained fevers. Indeed, a previous clinical study found no deleterious impact of transient fever (“fever spikes”) on LPR. Fourth, we used rectal temperature, which may underestimate actual brain temperature. Finally, although our study showed a relationship between fever, elevated LPR and outcome, our sample patient sample size did not allow us to perform independent associations between physiological variables and outcome, and the direction of cause and effect in this relationship remains unclear. The underlying mechanisms of cerebral metabolic distress after SAH are complex and elevated LPR may be attributable to various causes (eg, ischemia, edema); this is confirmed by higher ICP in patients with poor outcome. Our study suggests that fever may also contribute to increase cerebral metabolic distress, however it remains to be determined whether elevations of temperature and increased cerebral metabolic distress are merely markers of injury severity or they actively contribute to exacerbate brain injury and worsen outcome. Additional study is also needed to precisely evaluate the clinical significance of reduced LPR by induced normothermia after SAH and to determine, in larger patient samples, whether this may eventually translate into less neuronal injury and better outcome.

Despite these limitations, our data show that induced normothermia is associated with a reduction of elevated LPR and cerebral metabolic crisis in patients with poor grade SAH and refractory fever, irrespective of ICP level. These preliminary data also suggest that active fever control is a reasonable therapeutic strategy after SAH.

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Disclosures

None.

References

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