Postoperative Hyperthermia Is Associated With Cognitive Dysfunction After Coronary Artery Bypass Graft Surgery

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Background and Purpose—Temperature is a well-known modulator of experimental cerebral injury. We hypothesized that hyperthermia would be associated with a worsened cognitive outcome after coronary artery bypass graft surgery (CABG).

Methods—Three hundred consenting patients undergoing cardiopulmonary bypass for CABG had hourly postoperative temperatures recorded. The degree of postoperative hyperthermia was determined by using the maximum temperature within the first 24 hours as well as by calculating the area under the curve for temperatures >37°C. Patients underwent a battery of cognitive testing both before surgery and 6 weeks after surgery. By use of factor analysis, 4 cognitive domains (scores) were identified, and the mean of the 4 scores was used to calculate the cognitive index (CI). Cognitive change was calculated as the 6-week CI minus the baseline CI. Multivariable linear regression (controlling for age, baseline cognitive function, and temperature during cardiopulmonary bypass) was used to compare postoperative hyperthermia with the postoperative cognitive change.

Results—The maximum temperature within the first 24 hours after CABG ranged from 37.2°C to 39.3°C. There was no relationship between area under the curve for temperatures >37°C and cognitive dysfunction ($P=0.45$). However, the maximum postoperative temperature was associated with a greater amount of cognitive dysfunction at 6 weeks ($P=0.05$).

Conclusions—This is the first report relating postoperative hyperthermia to cognitive dysfunction after cardiac surgery. Whether the hyperthermia caused the worsened outcome or whether processes that resulted in the worsened cognitive outcome also produced hyperthermia requires further investigation. In addition, interventions to avoid postoperative hyperthermia may be warranted to improve cerebral outcome after cardiac surgery. (*Stroke*. 2002;33:537-541.)

Key Words: cardiopulmonary bypass ■ hyperthermia ■ temperature

Temperature, both hypothermia and hyperthermia, is a well-documented modulator of cerebral injury. Whereas hypothermia is considered to be protective, hyperthermia is disproportionately injurious to the ischemic brain.[1] Hyperthermia during and after ischemia has been documented to worsen both histological and functional outcome after experimental cerebral injury.[2–5] Clinical examples of its detrimental effect have been reported, with hyperthermia worsening the outcome after stroke.[6,7] Its effect on cardiac surgery–related cerebral injury has not been previously reported.

Cerebral injury, manifested by both stroke and cognitive dysfunction, has been well documented after cardiac surgery.[8–10] The effect of intraoperative temperature during cardiopulmonary bypass (CPB) has been studied, and although the results are variable, it is known to affect cerebral outcome.[11–13] The effects of postoperative temperature have not been well studied. Although we have previously demonstrated that hyperthermia is a common occurrence in the first 24 hours after cardiac surgery,[14] the purpose of the present study was to determine what effect postoperative hyperthermia would have on cognitive outcome. We hypothesized that hyperthermia in the first 24 hours after cardiac surgery would be associated with a worsened cognitive outcome 6 weeks after coronary artery bypass graft surgery (CABG).

Subjects and Methods

After Institutional Review Board approval and written informed consent, 300 patients undergoing elective CABG were studied.

Patients were excluded if they had a history of cerebrovascular disease (with residual deficits), uncontrolled hypertension, alcoholism, psychiatric illness, renal disease (creatinine >2 mg/dL), active liver disease, or less than a seventh grade education. The present study was originally designed to look at the effect of intraoperative CPB temperature on outcome, with patients randomly assigned to either normothermic (35.5°C to 36.5°C) CPB (warm group) or hypothermic (28°C to 30°C) CPB (cold group). The results of the influence of CPB temperature on outcome have been previously reported.[12] There was no apparent difference in outcome attributable to CPB temperature. So, for the purposes of this post hoc investigation of the effects of postoperative temperature, all patients (regardless of their original intraoperative temperature assignment) were analyzed together as a single cardiac surgical group.

The patients and the investigators performing the preoperative and postoperative neurocognitive assessments were blinded to the postoperative temperature profiles. Only the physicians directly involved with the perioperative care of these patients were potentially aware of the postoperative temperature.

Cognitive Testing

A standard baseline neurocognitive battery (for which the methodology has been reported previously[10]) was administered 1 day before surgery and then 6 weeks after surgery. The battery consisted of the following tests: (1) Short Story module of the Randt Memory Test, which requires subjects to recall the details of a short story both immediately after it has been read to them and after a 30-minute delay; (2) Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised, which is a test that requires subjects to repeat a series of digits that have been verbally presented to them both forward and, in a later independent test, reverse order; (3) Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised, in which subjects are allowed 90 seconds to perform a paper-and-pencil task that requires them to reproduce as many coded symbols as possible in blank boxes beneath randomly generated digits according to a coding scheme for pairing digits with symbols; (4) Modified Visual Reproduction Test from the Wechsler Memory Scale that measures short- and long-term figural memory requiring subjects to reproduce from memory several geometric shapes both immediately and after a 30-minute delay; and the (5) Trail Making Test (part B), which requires subjects to connect, by drawing a line, a series of numbers and letters in sequence (ie, 1-A-2-B) as quickly as possible.

Anesthetic and Surgical Techniques

Patients received a standard premedication of diazepam (0.1 mg/kg PO) and methadone (0.1 mg/kg PO) 90 minutes before the induction of anesthesia. Induction and maintenance of anesthesia were achieved with continuous infusions of midazolam and fentanyl.[15] Supplemental isoflurane (0.5% to 1.0%) was used as required to maintain heart rate and mean blood pressure within 25% of the preinduction values, and pancuronium was administered for neuromuscular paralysis.

The perfusion apparatus consisted of a membrane oxygenator (Cobe Laboratories), Sarns roller pump (3M Inc), and 40-μm arterial line filter (Pall Biomedical Products Co). CPB was nonpulsatile, with flows of 2 to 2.4 L · min^{-1} · m^{-2}. The CPB circuit was primed with crystalloid, and a hematocrit $\geq$0.18 was targeted (by the addition of packed red blood cells as necessary) during CPB. Arterial PCO_2 was maintained throughout CPB at 35 to 40 mm Hg (uncorrected for temperature), with the PaO_2 maintained at 150 to 250 mm Hg. A mean arterial pressure between 50 and 90 mm Hg during CPB was achieved by using intravenous phenylephrine and/or nitroprusside as required.

During CPB, the patients were rewarmed when the last distal coronary anastomosis was being placed, and they were separated from CPB when both the bladder and nasopharyngeal temperatures were >36°C. As part of the routine postoperative care, hourly temperatures (pulmonary artery catheter thermistor) were recorded in the intensive care unit record. Patients were actively warmed (by use of a forced-air convective warmer) if they arrived in the intensive care unit with a temperature <35.5°C. However, warming was

TABLE 1. Demographics

Age, y	61±10
Education, y	12±3
Male, %	84
Female, %	16
Diabetes, %	22
Hypertension, %	61
Grafts	3.3±0.9
LVEF, %	55±12
CPB time, min	103±29
Aortic cross-clamp time, min	53±18

LVEF indicates left ventricular ejection fraction.
Values are mean±SD or percentages.

discontinued when a temperature of 36.5°C was achieved. Hyperthermia was defined as the maximum temperature within the first 24 hours as well as the area under the curve for temperatures >37°C (AUC>37). Because variable degrees of hyperthermia are common after CABG, institutional clinical practice at the time of the study did not dictate any specific active therapy (such as active surface cooling or antipyretics, including nonsteroidal anti-inflammatory drugs) to treat the hyperthermia if it occurred during the first 24 hours. All patients received perioperative antibiotics for 48 hours.

Statistical Analysis

The methodology used to analyze the neurocognitive data has recently been described in detail.[10] To assess neurocognitive decline over time while minimizing the potential for neurocognitive testing overlap, a factor analysis was performed on the 10 baseline neurocognitive measures obtained from the battery of 5 cognitive tests used.[16,17] This method finds the commonality (overlap in testing) among the set of raw scores and constructs a smaller set of independent factor scores, with each representing a separate domain of cognitive function. The cognitive domains assessed are as follows: (1) verbal memory and language comprehension (short term and delayed); (2) attention, psychomotor processing speed, and concentration; (3) abstraction and visuospatial orientation; and (4) figural memory.

An overall cognitive function score (or cognitive index [CI]) at each test period was determined by adding together the independent factor scores. A cognitive change score was calculated by subtracting the baseline CI from the 6-week CI, thus representing a continuous measure of cognitive assessment. In addition, an overall binary "cognitive dysfunction" outcome was defined as a decline in performance of $\geq$1 SD in any of the independent domains.

The effect of postoperative temperature on 6-week CI was analyzed by using linear regression. A multivariable model, controlling for age, baseline cognitive function, years of education, and CPB temperature group assignment, was used to compare the maximum postoperative temperature and AUC>37 with the cognitive change score. The AUC>37, as opposed to AUC>38 or any other arbitrary hyperthermia cutoff, was chosen to facilitate the statistical analysis. It allowed the inclusion of data from all of the patients in the linear regression, whereas a progressively higher cutoff would invariably exclude some patients (who did not reach the hyperthermia threshold) from the analysis. In addition, the temperature profiles of any patients that did not return for the 6-week follow-up visit (nonreturners) were compared with those who did complete the 6-week follow-up (returners) by using a Wilcoxon 2-sided rank sum test. A value of $P \leq 0.05$ was considered significant.

Results

Demographics of the 300 patients are presented in Table 1. Two hundred ninety-eight patients completed preoperative neurocognitive testing, and 227 completed 6-week postoper-

TABLE 2.   Reasons for Missing 6-wk Cognitive Assessment

Reason	Patients, n
Transport	9
Interest	18
Stress	2
Health	20
Family	2
Time	5
No contact	5
Died	3
No show	1
Other	6

Transportation indicates difficulty in getting to the hospital for testing; interest, patient was not interested in repeating testing; stress, patient found testing too stressful; health, patient did not feel well enough to participate; family, family responsibilities prevented testing; time, patient was too busy; no contact, patient could not be contacted for follow-up; no show, patient failed to keep testing appointment; and other, patient expressed other reason for not participating.

ative testing. The reasons for the failure to complete the 6-week postoperative testing are detailed in Table 2. One hundred forty-nine patients were randomized to the warm CPB group, and 151 patients were randomized to the cold CPB group. The groups were similar with respect to postoperative temperatures. Specifically, the AUC>37 (6.8°C · h [warm group] versus 6.6°C · h [cold group], $P=0.68$) and maximum postoperative temperatures (39.2°C [warm group] versus 39.3°C [cold group], $P=0.99$) were not different between patients who were managed with either warm or cold CPB. As a result, all of the patients were considered as a single group for neurocognitive outcome analysis (although group assignment was included in the multivariable linear regression model). The temporal pattern of the temperatures in the first 24 postoperative hours is outlined in Figure 1. The peak temperature occurred from hours 6 to 10.

The overall incidence of cognitive dysfunction was 39% (89 of 227 patients). Factor analysis yielded 4 factors representing separate domains of cognitive function and accounting for 83% of the variance in the test battery. There was no relationship between AUC>37 and cognitive dysfunction ($P=0.45$). However, the maximum postoperative temperature was associated, albeit weakly, with a greater amount of cognitive dysfunction ($P=0.05$, $r^2=0.07$; Figure 2). There were no differences in either
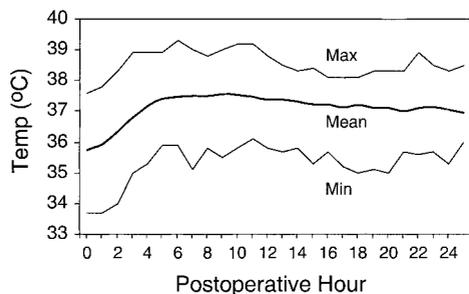

Figure 1. The minimum (Min), mean, and maximum (Max) temperature (Temp) determined by pulmonary artery catheter thermistor during the first 24 hours in 300 patients after CABG.
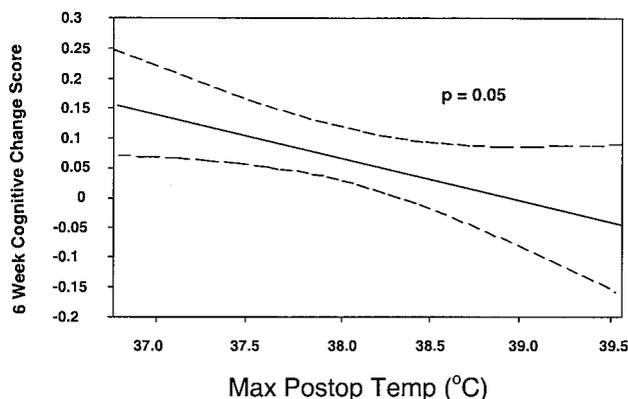

Figure 2. The association between maximum postoperative temperature (Max Postop Temp) and cognitive change score at 6 weeks after CABG in 300 patients.

AUC>37 or maximum temperature in the 6-week cognitive assessment of returners compared with the nonreturners (6.8±5.2°C · h [returners] versus 6.6±5.0°C · h [nonreturners], $P=0.92$]; 37.8±0.4°C [returners] versus 37.7±0.5°C [nonreturners], $P=0.80$)

Discussion

The issue of temperature and cerebral outcome after cardiac surgery has been extensively studied.[11–13,18,19] However, most previous studies have assessed the effect of intraoperative CPB temperature on various outcome parameters. The present study addresses the association between postoperative temperature and cerebral outcome after cardiac surgery. The novel finding of an association between postoperative hyperthermia and cognitive dysfunction stresses the importance of temperature management outside the time period of CPB.

Although no study has previously directly addressed the issue of hyperthermia and outcome, it has been examined indirectly. Grigore et al[20] have suggested the potential for hyperthermia to play a role in cerebral outcome in their study of the effect of differing rewarming strategies in patients after hypothermic CPB. In that study, patients who were rewarmed more slowly had lesser degrees of cognitive impairment 6 weeks after surgery. In addition, the patients who were rewarmed conventionally (and more rapidly) had higher overall maximum postoperative temperatures as well as a higher AUC>37. No temperatures in the postoperative period were reported.

With this adverse effect of hyperthermia, the important influence of temperature on cerebral responses to injury becomes readily apparent. There are several mechanisms by which hyperthermia may adversely affect the brain. Sternau et al[21] have demonstrated that the release of neurotransmitters (in excitotoxic quantities) is accentuated by hyperthermia. In their study of rats undergoing 20 minutes of forebrain (global) ischemia, hyperthermia resulted in a 37-fold increase in basal ganglionic glutamate release versus only a 21-fold increase after normothermic ischemia.[21] A greater increase in oxygen-derived free radical production after hyperthermic (versus normothermic) reperfusion after global ischemia has also been demonstrated.[22] Exaggerated increases in blood-brain barrier permeability occur during ischemia under hyperthermic conditions compared with

normothermic conditions.[23] Additionally, hyperthermia during ischemia increases ischemic depolarizations in the peri-infarct region and, as a consequence, increases infarct size.[24] Metabolically, compared with normothermia, hyperthermia has been demonstrated to increase intracellular acidosis after ischemic reperfusion; the recovery of ATP and other high-energy phosphates is also attenuated by hyperthermia.[25] Hyperthermia can also influence how protein kinases respond to ischemia.[26] Last, the cytoskeleton is sensitive to hyperthermia, with decreases in microtubule-associated protein (a cytoskeletal protein) that are due to calpain degradation.[27]

The above mechanisms, either alone or in combination, might be responsible for the effects of hyperthermia on outcome in experimental brain injury. Busto and colleagues[1,28] have demonstrated that as little as 1.5°C of hyperthermia (to 39°C) during a period of focal ischemia dramatically increases the size of cerebral infarction in rats. Interestingly, the injurious effect of hyperthermia was disproportionately greater than the relative protective effect of hypothermia, thus highlighting the lack of linearity to the protective and detrimental effects of temperature modulation in the brain. In a study by Kim et al,[4] delayed hyperthermia (as opposed to hyperthermia during the time of ischemia) had a similar effect of increasing infarct size after middle cerebral artery occlusion.[4] In addition, the ischemia induced by middle cerebral artery occlusion itself was also demonstrated to induce hyperthermia, most likely through damage to the hippocampus.[2] This would support the theory that the cerebral injury itself (such as that manifested as cognitive dysfunction) may lead to the hyperthermia, as opposed to the hyperthermia increasing the injury.

In conjunction with the experimental data mentioned above, specific reports of the detrimental effects of hyperthermia on clinical outcome have been reported. Hyperthermia after stroke has been associated with increased infarct size as well as increased morbidity and mortality. In patients admitted to the hospital after stroke, Reith et al[29] examined the relationship between temperature and infarct size, stroke severity, and mortality. They demonstrated a relative risk increase of 2.2 for each 1°C increase in body temperature. Their study was later supported by Castillo et al,[7] who demonstrated increased infarct volume, neurologic deficits, greater dependence, and a marked increase in mortality in patients with hyperthermia within the first 24 hours after stroke (15.8% hyperthermic and 1% normothermic, $P<0.001$).

There are several potential limitations of the present study. First, it is not clear whether the adverse association of hyperthermia with outcome is causal or temporal. That is, did the hyperthermia cause the worsened outcome, or did processes that resulted in the hyperthermia also independently impair cognitive outcome? The normal temperature response in the postcardiac surgical patient is not largely known or studied, but we speculate that it may be due to inflammatory processes initiated as a result of the interface between blood and the foreign surfaces of the CPB apparatus.[30] Clearly, systemic inflammation is related to increases in body temperature. In addition, inflammation is also known to exacerbate cerebral injury.[31,32] Whether cerebral inflammatory processes occur as a result of CPB is not clear.[33,34] The common link between temperature and outcome might relate to an inflammatory process initiated during CPB that

causes the brain injury and an independent hyperthermia, which then further exacerbates that injury. So in effect, this association that we have described may be both cause and effect.

A further limitation is the site of temperature monitoring. We chose the pulmonary artery thermistor because this was easily accessed in most patients. It is a reasonable estimate of core/brain temperature in patients in whom temperature fluxes are gradual. However, gradients between temperature sites during CPB have been reported. We[35] and others[36] have demonstrated a gradient during CPB between nasopharyngeal and jugular bulb sites. However, this is unlikely to be a factor after recovery from CPB, when normal circulation has been restored and no active warming is under way. Others have shown in patients with traumatic brain injury that a gradient may exist between intracerebral and extracerebral temperature sites.[37] However, cerebral injury after CPB is less likely to be as severe as that in trauma patients whose intracerebral temperature is likely partially related to reductions in cerebral blood flow. Cerebral blood flow after CPB is relatively normal.[38]

A final limitation relates to the lack of follow-up cognitive testing in 71 patients. Although this is similar to the follow-up rates reported by others in similar types of studies,[39] it could potentially bias the results. However, when one examines the postoperative temperature profiles between the returners and the nonreturners, there were no differences; thus, regarding the degree of hyperthermia that they experienced, it is likely that those who completed the testing accurately represented those who did not complete the testing.

In conclusion, we have described an association between peak postoperative temperature and neurocognitive decline after cardiac surgery. This finding may have several potential implications for future research. Interventions to avoid postoperative hyperthermia may be beneficial in improving cerebral outcome after cardiac surgery. Alternatively, the occurrence of hyperthermia may identify the patient in whom injury has or is likely to have occurred; this patient is representative of a unique group of patients who can be of use in the study of potential neuroprotective strategies.

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