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Perioperative Hypothermia (33°C) Does Not Increase the Occurrence of Cardiovascular Events in Patients Undergoing Cerebral Aneurysm Surgery: Findings from the Intraoperative Hypothermia for Aneurysm Surgery Trial

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Abstract

Background—Perioperative hypothermia has been reported to increase the occurrence of cardiovascular complications. By increasing sympathetic nervous system activity, perioperative hypothermia also has the potential to increase cardiac injury and dysfunction associated with subarachnoid hemorrhage.

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Summary Statement: In 1,000 patients undergoing cerebral aneurysm surgery, randomization to intraoperative hypothermia (33.3 ± 0.8°C) was not associated with an increased occurrence of cardiovascular events as compared to intraoperative normothermia (36.7 ± 0.5°C)

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Methods—The Intraoperative Hypothermia for Aneurysm Surgery Trial randomized patients undergoing cerebral aneurysm surgery to intraoperative hypothermia (n = 499, 33.3 ± 0.8°C) or normothermia (n = 501, 36.7 ± 0.5°C). Cardiovascular events (hypotension, arrhythmias, vasopressor use, myocardial infarction, *etc*.) were prospectively followed until 3 month follow-up and were compared between hypothermic and normothermic patients. A subset of 62 patients (hypothermia, n = 33; normothermia, n = 29) also had preoperative and postoperative (within 24 h) measurement of cardiac troponin-I and echocardiography to explore the association between perioperative hypothermia and subarachnoid hemorrhage-associated myocardial injury and left ventricular function.

Results—There was no difference between hypothermic and normothermic patients in the occurrence of any single cardiovascular event or in composite cardiovascular events. There was no difference in mortality (6%) between groups and there was only a single primary cardiovascular death (normothermia). There was no difference between hypothermic and normothermic patients in post- *vs.* preoperative left ventricular regional wall motion or ejection fraction. Compared with preoperative values, hypothermic patients had no postoperative increase in cardiac troponin-I (median change 0.00 μg/L) whereas normothermic patients had a small postoperative increase (median change + 0.01 μg/L, $P = 0.038$).

Conclusion—In patients undergoing cerebral aneurysm surgery, perioperative hypothermia was not associated with an increased occurrence of cardiovascular events.

Introduction

There is continued interest in the potential benefit of mild systemic hypothermia in the treatment of various neurologic insults such as stroke, head trauma, and anoxic/ischemic brain injury after cardiac arrest.[1] Counterbalancing potential neurological benefits of hypothermia are several known or potential risks. For example, in the perioperative period, mild systemic hypothermia has been reported to increase occurrence of various cardiovascular events two- to six-fold.[2-4] The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was a multicenter, prospective, randomized, partially-blinded trial designed to determine whether mild intraoperative systemic hypothermia (33°C) would improve neurological outcome in patients undergoing surgery to treat acutely ruptured intracranial aneurysms as compared with intraoperative normothermia.[5] As part of trial safety monitoring, IHAST prospectively followed events in other organ systems, including the cardiovascular system. The aim of the current study is to test the hypothesis that intraoperative hypothermia was associated with a greater occurrence of cardiovascular events.

Some patients with subarachnoid hemorrhage (SAH) have signs of SAH-associated myocardial injury and/or dysfunction such as positive myocardial enzymes, regional wall motion abnormalities, and left ventricular (LV) dysfunction.[6] These abnormalities appear to be mediated by excessive catecholamine activity, both systemically and at cardiac sympathetic nerve terminals.[7,8] Because perioperative hypothermia increases postoperative catecholamine levels,[9] perioperative hypothermia may worsen SAH-associated cardiac abnormalities. To explore whether perioperative hypothermia increased SAH-associated cardiac abnormalities, a subset of IHAST patients underwent pre- and postoperative assessments of myocardial injury (cardiac troponin-I) and LV function (echocardiography).

Materials and Methods

Details of IHAST design, patient eligibility, protocols, and outcome assessment have been published previously.[5] In brief, between February 2000 and April 2003 nonpregnant adults with SAH and an angiographically-confirmed intracranial aneurysm scheduled to undergo

surgical treatment within 14 days of hemorrhage were eligible to participate. Other major inclusion criteria included a preoperative World Federation of Neurological Surgeons (WFNS) class of I, II, or III[10] and not being tracheally intubated at the time of study enrollment. IHAST protocols were approved by the Human Subjects' Committees at each participating center (n = 30) and written informed consent was obtained from either patients or their families.

Anesthesia and Temperature Management

Anesthesia was induced with thiopental or etomidate and maintained with isoflurane or desflurane, fentanyl or remifentanil, and nitrous oxide or air with oxygen. Selection of intraoperative monitoring was determined by the preferences of each operating team although all patients had intraarterial blood pressure monitoring. After induction of general anesthesia, patients were randomized to one of two groups: 1) hypothermia (target esophageal temperature 33.0°C) or 2) normothermia (target esophageal temperature 36.5°C), which were achieved with surface techniques. Knowledge of intraoperative temperature was limited to each patient's anesthesiologist; surgeons were not informed of patient temperature. Intraoperative heart rate and systemic blood pressure, and methods used to achieve desired levels for these variables (*e.g.*, vasoactive agents or fluids), were determined by each patient's anesthesiologist and operative team. Other medications such as neuromuscular blockers, antiemetics and analgesics were similarly determined. Rewarming of hypothermic patients began after the last aneurysm had been secured. Based on a pilot study,[11] it was anticipated that many patients assigned to hypothermia would not be completely rewarmed by the end of surgery. IHAST protocols recommended that patients who were still hypothermic (<35.5°C) at the end of surgery should remain intubated and sedated with propofol[12] until normothermia was restored. In all patients, the goal was to return the patient to a state in which neurologic assessment and extubation were possible as soon as possible after the end of surgery.

IHAST Data Collection and Safety Monitoring

All IHAST data collection, pre- and postoperative management decisions, and outcome assessments were made by individuals who had no knowledge of temperature group assignment. Preoperative data collection included patient demographics and pre-SAH medical history. Information regarding the characteristics of the ruptured aneurysm (location, angiographic diameter) and its immediate effects (amount of subarachnoid blood [Fisher Scale],[13] WFNS class,[10] and National Institutes of Health Stroke Scale[14]) were recorded prior to surgery. Postoperative management was not standardized, but all aspects of treatment and patient condition were prospectively documented daily from enrollment to postoperative day 14 or discharge, whichever came first. A final outcome assessment was conducted approximately 3 months after surgery.

At every patient encounter, patients were assessed for the occurrence of any of 106 predefined events or procedures, collectively referred to as intercurrent events (IE's). IE's were categorized as occurring in one of nine body systems: 1) whole body/general, 2) cardiovascular, 3) respiratory, 4) digestive, 5) endocrine/metabolic, 6) neurologic/ neurosurgical, 7) urogenital, 8) coagulation/hematologic, and 9) other/unclassified. Across all nine IE categories, there were a total of 68 specific events and 38 procedures/ interventions which were followed. Each IE had pre-defined diagnostic criteria based on published guidelines, standards, or consensus statements available at the start of the trial. Each IE was classified by local investigators as having its onset during one of five intervals: 1) preoperative (prerandomization), 2) intraoperative, 3) within the first 2 h after surgery, 4) postoperatively (from 2 h after surgery until 14 days or discharge), or 5) from discharge to final 3-month follow-up.

The severity and clinical impact of each IE was classified by local investigators as either 1) mild, 2) moderate, 3) severe, or 4) fatal. Mild events were defined as being well tolerated and not appearing to substantially influence the patient's overall clinical course. Moderate events were sufficient to interfere with the patient's recovery; usually some new treatment was necessary and/or the duration of hospitalization was slightly prolonged. Severe events were life threatening, permanently disabling, or substantively prolonged in-patient hospitalization. IE's with a rating of death were those that resulted in patient death.

A predefined subset of IE's (n = 27) were designated as “Indicator” IE's. Indicator IE's were events that prior studies had suggested might occur more often in patients with intraoperative hypothermia, such as major cardiovascular events,[2-4] infection,[15] or bleeding,[16] and/or events associated with major neurologic morbidity (*e.g.*, intracranial hemorrhage, intracranial hypertension, brain swelling, cerebral infarction). The occurrence of any Indicator IE, regardless of severity, or any IE classified by local investigators as severe or associated with a patient death, required a report to the IHAST Clinical Coordinating Center (CCC) within one work day.

The IHAST CCC monitored all IE reports. All CCC personnel were blinded to each patient's temperature assignment and all intraoperative temperature data. All IE reports were reviewed by a CCC physician (B.H.) who verified diagnostic criteria were met and that all associated IE's were coded and documented in accordance with IHAST procedures. The CCC communicated with local investigators to resolve all apparent discrepancies and reporting errors. The CCC maintained a real-time database of all IE reports. This database was monitored by the Data Management Center and was freely available to the trial's Physician Safety Monitor who was authorized to stop the trial at any time if any disproportionate or unexpected risk was suspected.

Any patient death required local investigator to provide a supplemental report describing the circumstances and causes of the patient's death. For each patient who died, a CCC physician (B.H.) reviewed all IHAST case report forms and collected all available supplemental supporting documents (*e.g.*, autopsy reports) to prepare a detailed clinical summary. The only information that was excluded from this review was patient intraoperative temperature. Based on this review, primary and secondary causes of death and corresponding International Classification of Disease (ICD)-10 codes were assigned. The clinical summaries were immediately provided to the IHAST Principal Investigator (M.T.) and Physician Safety Monitor.

Cardiovascular Events

Diagnostic criteria for 26 IHAST cardiovascular IE's are summarized in Appendix 2. Eight of the 26 cardiovascular events (*e.g.*, myocardial infarction, ventricular arrhythmias, vasopressors to support the systemic circulation, *etc*.) were also designated as Indicator IE's. Because both hypotension and hypertension can be deliberately utilized in the treatment of cerebral aneurysm patients, these two events were classified as either intended or not intended. Vasopressor use was classified as for cardiovascular indications (*e.g.*, hypotension, low cardiac output), neurological indications (*e.g.*, to support cerebral perfusion) or for other indications.

For cardiovascular events occurring in 20% of normothermic patients, IHAST had sufficient statistical power (alpha = 0.05, beta = 0.20) to detect an absolute increase of 8% (relative increase 28% ÷ 20% = 1.40) in hypothermic patients. For cardiovascular events occurring in 10% and 5% of normothermic patients, IHAST had sufficient statistical power to detect an absolute increase of 6.5% and 5%, and relatives increase of 1.65 and 2.00 in hypothermic patients, respectively.

Myocardial Injury and Dysfunction Sub-Study

With approval of the IHAST Data and Safety Monitoring Board, in December, 2000 twelve IHAST centers were invited to participate in a supplementary exploratory study, the Myocardial Injury and Dysfunction Sub-Study (MIDS). Seven centers accepted (see Appendix 1) and, in these centers, informed consent documents included additional information regarding MIDS procedures. The aim of MIDS was to determine if perioperative hypothermia was associated with increases in troponin release, left ventricular dysfunction, or regional wall motion abnormalities.

Patients enrolled in MIDS (n = 62), underwent pre- and postoperative blood collection and transthoracic echocardiography (TTE). Preoperative TTE and serum collection was obtained no more than 24 h prior to surgery and both procedures were repeated within 8-24 h after surgery. TTE system settings were chosen to maximize resolution of LV endocardial borders, using harmonic imaging when available. During both TTE studies, the following echocardiographic views were acquired: parasternal long axis, parasternal short axis (mid-papillary level), apical 4-chamber, apical 2-chamber, and apical 3-chamber. No identifying information was included with the TTE images other than the IHAST patient identification number.

Each echocardiogram was sent to the IHAST CCC and assigned a code number to blind the core echo laboratory to patient randomization status, the timing of the exam relative to surgery, and all other clinical information. All coded TEE studies were interpreted by a single experienced echocardiographer (JZ). Left ventricular ejection fraction (LVEF) was measured using standard methodology.[17] Regional LV function was defined using a 16 segment wall motion score in which each segment was graded as either 1 (normal), 2 (hypokinetic), or 3 (akinetic or dyskinetic).[17] From these 16 individual scores, a mean regional wall motion score (RWMS) was calculated. Final TTE results were sent to the IHAST CCC, decoded, and included in the database.

In MIDS patients, 10 ml of blood was obtained pre- and postoperatively using serum separator tubes. After standing upright for 30 min, each tube was centrifuged for 5 min and the serum was placed into a polypropylene tube and stored at -70°C. Each tube was labeled with a code number and no patient identifiers. At the conclusion of the study, all samples were shipped on dry ice to the University of Western Ontario, thawed, and serum levels of cardiac troponin-I (cTnI) were measured (Beckman Coulter Access 2, Chemiluminescence Immunoassay, Beckman Coulter Canada, Incorporated; Mississauga, Ontario, Canada). The lower limit of detection of this assay was 0.03 μg/L and this value was assigned to all patients when no activity was detected. Final cTnI results were sent to the IHAST CCC, decoded, and included in the database.

MIDS prestudy power analysis was based on data indicating 25% of SAH patients would have a least some preoperative wall motion abnormalities (RWMS > 1.0 with standard deviation of 0.3).[6] We assumed that only those patients with preoperative RWMS > 1.0 would be at significant risk to develop new or worsened wall motion, and that hypothermia would increase risk relative to normothermia. To detect a between-group difference of 0.4 units in mean RWMS (alpha = 0.05, beta = 0.20) would require 11 patients per group, or a total of 22 patients with preoperative wall motion abnormalities. Therefore, the necessary MIDS sample size was estimated to be (22 × 4) 88 patients.

Statistical Methods

All data entry was performed by the Data Management Center at the University of Iowa. Statistical analyses were performed on SAS 9.1.3 Service Pack XP_PRO Platform (SAS Institute, Inc., Cary, NC). Power analyses were performed using nQuery Advisor, 7.0

(Statistical Solutions, Ltd., Cork, Ireland). All analyses were based on intention to treat. The univariate tests utilized included the Fisher's Exact test, and Wilcoxon Rank Sum test depending on the characteristics and distribution of the data. In all analyses, all *P*-values are two-sided with $P \leq 0.05$ was the threshold for a statistically significant difference or association, without adjustment for multiple comparisons.

For the entire IHAST population (n = 1000), pre- and postoperative variables, and the occurrence cardiovascular events were compared between hypothermic and normothermic patients. For this analysis, cardiovascular events were classified as having their onset in one of two periods: 1) Perioperative—events with their onset intraoperatively or during the first 2 h after surgery, or 2) Postoperative—events with their onset more than 2 h after surgery until the 3 month outcome assessment. For individual event analysis, cardiovascular events were classified as either present (any severity) or absent. To increase statistical power to detect differences between temperature groups, cardiovascular events were grouped *post hoc* into various composite categories (*e.g.*, any cardiovascular event, any indicator event, *etc*.). For the calculation of composite cardiovascular events, four of the 26 cardiovascular IE's were excluded. Hypertension and hypotension that were intended were excluded. Electrocardiography and echocardiography were also excluded because they are procedures and do not necessarily indicate a cardiovascular event occurred. For all composite events, odds ratios and 95% confidence intervals were also calculated, using normothermia as the reference group.

For the MIDS population (n = 62), pre- and postoperative values for cTnI, RWMS, and LVEF were compared between hypothermic and normothermic patients. In addition, using paired pre- and postoperative values, the change in each of these variables was calculated and compared between hypothermic and normothermic patients. Because there is no established threshold value for a clinically significant cTnI value in the setting of SAH, absolute cTnI values were compared.

Results

Entire IHAST Population

The characteristics of the entire IHAST population (n = 1,000) are summarized in table 1. With one exception, patients randomized to hypothermia (n = 499) and normothermia (n = 501) were equivalent in terms of age, sex, pre-SAH cardiovascular history, preoperative neurologic condition, severity of SAH, and cerebral aneurysm characteristics. A history of pre-SAH coronary artery disease (CAD) was slightly more common in patients randomized to hypothermia than those randomized to normothermia, 7% *vs.* 4%, respectively, $P = 0.017$.

Temperature on arrival to the operating room did not differ between patients randomized to hypothermia and normothermia. Patients randomized to intraoperative hypothermia had a core temperature of 33.3 ± 0.8°C at time of first aneurysm clipping. Although rewarming of hypothermic patients began after final clip placement, core temperatures increased by only ~1°C by the end of surgery (34.2 ± 0.9°C). Consequently, 60% of those randomized to hypothermia remained intubated on arrival to the postoperative care area as compared to 24% of those assigned to normothermia, $P < 0.001$. Continued postoperative rewarming resulted in core temperatures that were nearly normal by 2 h after surgery. However, at 2 h after surgery, patients randomized to hypothermia continued to be intubated more often than patients randomized to normothermia, 25% *vs.* 13%, respectively, $P < 0.001$. At 24 h after surgery, intubation was equally common in both groups, ~10%.

As summarized in tables 2 and 3, during the perioperative period (during surgery and the first 2 h after surgery) the most common cardiovascular events were vasopressor

administration (25% of patients) and unintended hypertension (7% of patients). During this period, arrhythmias and unintended hypotension were each reported in less than 5% of patients. In the postoperative period, the most common cardiovascular events were vasopressor administration (22% of patients), congestive heart failure or pulmonary edema (9% of patients) and unintended hypertension (9%). Nonventricular arrhythmias (6%), unintended hypotension (4%), and myocardial infarction and ventricular arrhythmias (1%) were infrequent postoperative cardiovascular events.

As shown in table 2, there were no differences between hypothermic and normothermic patients in the occurrence of any single cardiovascular event, during either the peri- or postoperative period. Likewise, as summarized in table 3, the number of patients who experienced any cardiovascular event, received any vasopressor, experienced any "indicator" cardiovascular event, any cardiac morbidity (myocardial infarction, pulmonary edema, ventricular arrhythmias or cardioversion/defibrillation) or death did not differ between hypothermic and normothermic patients.

Sixty-one patients died between randomization and 3-month follow-up. The primary causes of death were neurological in 46 patients (75%), respiratory in 6 (10%), pulmonary embolus in 4 (7%), sepsis in 4 (7%) and cardiovascular in 1 patient (<2%). In the latter patient, deliberate intraoperative hypotension was used to reduce aneurysm wall tension under normothermic conditions. The patient acutely developed ventricular fibrillation and resuscitation was unsuccessful. An autopsy revealed previously unrecognized severe three-vessel atherosclerotic CAD. The presumptive mechanism of death was hypotension-induced myocardial ischemia and arrhythmia. Postoperatively, 14 patients (hypothermia, n = 8; normothermia, n = 6) had 30 postoperative cardiovascular IE's rated by local investigators as fatal. However, none of these cardiovascular events were a direct or primary cause of death. Two patients with severe postoperative neurologic injury experienced cardiac arrest of unknown cause. One patient with severe postoperative neurological injury and herniation experienced hypotension that was considered to contribute to death. Finally, one patient with systemic sepsis had bradycardia that was considered to exacerbate multi-system failure. One patient died from sepsis shortly after 3-month follow-up for a total of 62 deaths in the trial.

MIDS Population

The pre- and intraoperative characteristics of MIDS patients (n = 62) did not differ from the rest of the IHAST population (n = 938), with the sole exception that perioperative vasopressor use was more common in MIDS patients than non-MIDS patients, 60% *vs.* 23%, respectively, $P < 0.001$. The occurrence of cardiovascular events in MIDS patients did not significantly differ from the rest of the IHAST population (data available but not shown). Patient and aneurysm characteristics did not differ between MIDS patients assigned to hypothermia (n = 33) and normothermia (n = 29), and the occurrence of cardiovascular events did not differ between MIDS patients assigned to hypothermia and normothermia (data available but not shown).

As summarized in table 4, there were no significant differences between hypothermic and normothermic MIDS patients in preoperative LVEF, RWMS, or cTnI, When calculated as absolute values, hypothermic MIDS patients exhibited no net change in cTnI between pre- and postoperative samples (median change 0.00 μg/L) whereas, in normothermic MIDS patients there was a tiny increase (median 0.01 μg/L). The difference in cTnI change between temperature groups achieved statistical significance, $P = 0.038$.

Discussion

Primary Findings

With 1,000 patients, IHAST is the largest study of intraoperative hypothermia yet conducted. Cerebral aneurysm surgery patients were randomized to mild systemic hypothermia (33°C) or normothermia, and outcomes were prospectively assessed by examiners unaware of intraoperative temperature utilizing predefined diagnostic criteria. Perioperative hypothermia was not associated with improved neurological outcome 3 months after surgery.[5] The key finding of the current study is that perioperative hypothermia was not associated with an increase in the occurrence of cardiovascular events.

Intraoperatively, and for the first 2 h after surgery (perioperative), hypothermic patients had no greater incidence of arrhythmias or hypotension, and no greater need for vasopressors than patients who were normothermic. This is consistent with studies showing that, in anesthetized patients, systemic hemodynamics (*e.g.* mean arterial pressure, systemic vascular resistance, heart rate[18]) and left ventricular performance (*e.g.*, cardiac index,[18], fractional shortening, stroke volume index[19]) are maintained near normothermic values during mild systemic hypothermia (32.0-33.5°C). Likewise, other than sinus bradycardia, hypothermia-related arrhythmias are not commonly observed at core temperatures greater than 32°C.[20-25]

In the perioperative period 250 patients (25%) received a vasopressor to support the cerebral circulation (~20%) and/or systemic circulation (~9%). This frequency of vasopressor administration is nearly identical to that reported by Lai *et al.* in a series of 100 patients undergoing cerebral aneurysm surgery (29%).[26] In IHAST, in only 9 of 250 patients (4%) was perioperative vasopressor administration considered by the anesthesiologist to be a severe event. Using propensity analysis, Fellahi *et al.* reported that, in patients undergoing cardiac surgery, perioperative vasopressor use (primarily dobutamine) was associated with less favorable outcome (ventricular arrhythmias, myocardial infarction, death).[27] This was not the case in the IHAST population. There was no association between perioperative vasopressor administration and either postoperative ventricular arrhythmias ($P = 1.00$) or postoperative myocardial infarction ($P = 1.00$). Similarly, in a multivariate model that included ten standard covariates (*e.g.*, age, preoperative WFNS class, aneurysm location, Fisher score, *etc*.),[28] there was no significant association between perioperative vasopressor administration and mortality ($P = 0.09$); data available but not shown.

There was one cardiovascular death in the perioperative period, but this was not related to hypothermia. Rather, death appeared to be related to the use of deliberate (intended) hypotension in a normothermic patient with unrecognized three-vessel coronary artery disease. Although previously a common practice, induced hypotension is now infrequently used in cerebral aneurysm surgery. In IHAST, deliberate intraoperative hypotension was utilized in 16 of 30 centers and in less than 5% of patients. In a multivariate model that included ten standard covariates (*e.g.*, age, preoperative WFNS class, aneurysm location, Fisher score, *etc*.),[28] there was no significant association between perioperative intended hypotension and mortality ($P = 0.90$); data available but not shown.

In the postoperative period, vasopressor administration remained as the most frequent cardiovascular event (~20% of patients), given primarily to support the cerebral circulation. Postoperative congestive heart failure or pulmonary edema occurred in approximately 9% of patients. Rather than ischemic left ventricular failure, these two events are most likely the linked consequence of hypertensive hypervolemic hemodilution (“triple H therapy”) which is commonly used to increase systemic blood pressure and/or cardiac output prevent or treat post-SAH cerebral vasospasm. Solenski *et al.* reported pulmonary edema occurred in 29%

of postoperative SAH patients in whom intentional hypervolemia and/or induced hypertension were routinely employed.[29] The lesser rate of pulmonary edema observed in IHAST was possibly due to a lesser rate of symptomatic vasospasm than that observed by Solenski *et al.* (23% *vs.* 46%, respectively) and, consequently, less frequent and/or aggressive hyperdynamic therapy in IHAST. Consistent with that hypothesis, Kim *et al.* reported pulmonary edema in postoperative SAH patients decreased from 14% to 6% when less aggressive hypervolemic therapy was utilized.[30] In IHAST, postoperative congestive heart failure or pulmonary edema was rated as mild or moderate in 80 of 94 (85%) patients.

In IHAST the incidence of postoperative myocardial ischemia/infarction (1%), ventricular arrhythmias (1%), and cardiogenic shock (0%) was low and did not differ between patients randomized to hypothermia and normothermia. Nearly identical rates for these three events were reported by Solenski *et al.* in a group of 455 surgical SAH patients.[29] In IHAST, all postoperative myocardial infarctions were nonfatal.

Perioperative Hypothermia and Cardiovascular Events

In IHAST, hypothermia was not associated with the increased occurrence of any single cardiovascular event or any composite cardiovascular event. In stark contrast, three previous studies reported that perioperative hypothermia increased the incidence of cardiovascular complications.[2-4] These previous studies have been widely cited and have been used as evidence to support standards regarding maintenance of perioperative normothermia.[†‡] Given the impact and influence of prior studies, and the absence of increased cardiovascular events with perioperative hypothermia in the IHAST population, a thorough comparison of these apparently contradictory studies is warranted.

In 1993, Frank *et al.* reported a nonrandomized study of 100 patients undergoing lower extremity vascular surgery.[2] Patients with unintentional hypothermia (recovery room temperatures <35°C, n = 33) had, when compared to patients with temperatures ≥35°C (n = 67), a greater incidence of myocardial ischemia on Holter monitoring (36% *vs.* 13%) and a greater incidence of angina (18% *vs.* 2%) during the first 24 h after surgery.[2] There was, however, no significant difference in the occurrence of myocardial infarction (~4%) or major morbidity (~12%) between hypothermic and normothermic patients. In 1995, Bush *et al.* reported a nonrandomized study of 262 patients undergoing abdominal aortic aneurysm surgery.[3] Patients with unintentional hypothermia (postoperative temperatures < 34.5°C, n = 66) had, when compared to patients with temperatures ≥ 34.5°C (n = 196), a greater need for postoperative vasopressors (11% *vs.* 6%) and inotropes (35% *vs.* 13%), and a greater incidence of myocardial infarction (8% *vs.* 4%; not significant).[3] Finally, in 1997, Frank *et al.* reported a randomized trial of intraoperative temperature management in 300 patients undergoing thoracic, abdominal, or vascular surgery.[4] Routine thermal management resulted in hypothermia (35.4°C in recovery) whereas supplemental intraoperative warming maintained normothermia. Hypothermic patients had a greater incidence of cardiac morbidity (6% *vs.* 1%) and ventricular tachycardia (8% *vs.* 2%) during the first 24 h after surgery.[4] There was, however, no significant difference in the incidence of electrocardiographic myocardial ischemia (~6%) or myocardial infarction (< 1%).

[†]The Joint Commission. Specifications Manual for National Hospital Inpatient Quality Measures, version 3.0c, Effective October 1, 2009. SCIP-Inf-10, Surgery Patients with Perioperative Temperature Management. http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/Current+NHQM+Manual.htm (Accessed January 22, 2010).

[‡]National Institute for Health and Clinical Excellence. NICE guidance aims to prevent hypothermia in patients undergoing surgery. http://www.nice.org.uk/nicemedia/pdf/2008029PerioperativeHypothermia.pdf (Accessed January 22, 2010)

The most obvious differences between IHAST and prior reports are with regard to study design and patient characteristics. In two of the three prior studies, intra- and postoperative hypothermia were not intentional.[2,3] In these two studies the development of hypothermia may have been the consequence of less favorable intraoperative conditions. For example, in the study by Bush *et al.*, patients who became hypothermic intraoperatively had larger aortic aneurysms, greater operative time, greater fluid requirements, greater blood loss, and greater transfusion requirements.[3] Some or all of these factors may have contributed to less favorable postoperative cardiovascular outcomes rather than hypothermia *per se*.

The other important difference is that patients in prior studies had a much greater incidence of CAD. In the 1997 study by Frank *et al.*, 49% of their patients had known CAD,[4] as compared to 5% in the IHAST population. Frank *et al.* proposed that, in their patients, hypothermia-associated cardiovascular morbidity was largely the consequence of increased postoperative adrenergic responses (*e.g.*, hypertension and tachycardia) after emergence from anesthesia. During surgery and anesthesia, Frank *et al.* observed the occurrence of myocardial ischemia and ventricular arrhythmias was equivalent between hypothermic and normothermic patients.[4] However, upon emergence, hypothermic patients more commonly developed hypertension, probably in response to increased circulating catecholamines.[4] This hypothesis was based on their prior observation that hypothermic surgical patients (35.3°C in recovery) had significantly greater postoperative plasma norepinephrine concentrations and systemic arterial pressure than normothermic patients.[9]

Subsequently, Frank *et al.* showed in healthy volunteers that a 1°C decrease in core temperature increased plasma epinephrine by 68-120%, norepinephrine by 230-251%, rate-pressure product by 25-33%, cardiac output by 23%, and coronary blood flow by 20%.[31,32] Notably, in healthy patients, hypothermia did not change the relationship between rate-pressure product and coronary perfusion.[32] In other words, increased myocardial work and myocardial oxygen requirements provoked by mild systemic hypothermia were matched by increased coronary blood flow and did *not* induce myocardial ischemia. In contrast, in patients with flow-limiting coronary stenoses, coronary blood flow may not be able to increase sufficiently to meet increased myocardial oxygen demands triggered by hypothermia-induced adrenergic responses. Frank *et al.* have shown that beta-blockade decreases hypothermia-induced systemic catecholamines and eliminates hyperdynamic cardiovascular responses.[32]

Therefore, the collective evidence indicates hypothermia-related cardiovascular morbidity is probably due to adrenergically-mediated hemodynamic responses occurring during or after emergence from anesthesia which, *in patients with CAD*, can increase myocardial oxygen demands to the point of ischemia. In addition, some studies indicate patients with CAD may also exhibit a pathological increase in coronary vascular resistance in response to cold stimuli, perhaps due to impaired coronary artery endothelial function.[33, 34] If so, it is possible this response might also contribute to hypothermia's adverse cardiovascular effects in patients with CAD.

Because 95% of IHAST patients had no prior history of CAD, the IHAST population was at low risk of cardiovascular complications on the basis of adrenergically-mediated increases in cardiac work. In the IHAST population, the incidence of perioperative hypertension was relatively low (~7%) and was equivalent between hypothermic and normothermic patients. Breslow *et al.* showed that general anesthesia attenuates sympathetic activity and catecholamine responses to noxious stimuli.[35] By maintaining sedation/anesthesia during postoperative rewarming, the cardiovascular effects of postoperative hypothermia may have been attenuated in the small fraction of IHAST patients who had CAD.

Accordingly, we suggest that the evidence upon which perioperative temperature management standards are based should be reconsidered with regard to the risks of cardiovascular complications with mild perioperative hypothermia. Maintenance of perioperative hypothermia to decrease cardiovascular complications in patients with CAD may be reasonable. Maintenance of perioperative hypothermia may be prudent for other reasons as well, such as decreasing perioperative blood loss and/or wound infection.[36] However, in patients with low a risk of CAD, our findings indicate that perioperative hypothermia does not increase the occurrence of cardiovascular events.

SAH-Associated Myocardial Injury and Dysfunction

Multiple studies have shown that some SAH patients may have signs of acute myocardial injury and/or left ventricular dysfunction[37] and that these abnormalities may independently contribute to less favorable outcomes.[38, 39] In a study of 182 SAH patients, Zaroff *et al.* reported LV regional wall motion abnormalities were present in 25% of patients, elevated troponin (cTnI > 1 μg/L) was present in 13%, and decreased LVEF (≤ 50%) was present in 12%.[6] The weight of current evidence supports the concept that SAH-associated cardiac injury is adrenergically mediated, triggered by pathological release of catecholamines at cardiac sympathetic nerve terminals at the time of the initial SAH.[8] The result is widely distributed, but highly focal, form of microscopic myocardial injury, referred to as contraction band necrosis.[40-46] Both clinically[47] and in animal SAH models,[42,48] contraction band necrosis is decreased by β-blockers[48] and/or drugs that deplete norepinephrine stores.[42] Neil-Dwyer *et al.* reported SAH patients randomized to receive ß-blockers appeared to have decreased myocardial enzyme release[49] and improved short-term and long-term mortality and neurologic outcome.[49-51]

IHAST-MIDS was an exploratory study to determine whether perioperative hypothermia would affect the course of SAH-associated cardiac injury and dysfunction. Unexpectedly, the IHAST-MIDS population differed substantially from previous reports of SAH patients[6] by having an extremely low incidence of preoperative myocardial injury/dysfunction. In the MIDS population, preoperative regional wall motion abnormalities were present in only 5% (3/61), elevated preoperative troponin (cTnI >1 μg/L) was present in 2% (1/51), and preoperative LVEF <50% was present in only 2% (1/54). These rates were 5-6 fold less than had been expected.[6] The most likely explanation for the very low incidence of SAH-associated cardiac abnormalities in MIDS patients was their good preoperative neurologic status; 94% (58/62) of patients were WFNS I or II. Both SAH-associated troponin release[52] and regional wall motion abnormalities[53] are associated with poor neurologic grades (Hunt and Hess grades of 3 or more). Therefore, it appears patients who suffer the greatest degrees of neurologic injury with SAH are those most likely to experience SAH-associated myocardial injury and dysfunction.

In retrospect, because the preoperative incidence of SAH-associated myocardial injury and dysfunction was so much less than expected, MIDS was underpowered to address the effect of perioperative hypothermia on the pathophysiology of SAH-associated cardiac injury. Therefore, this question remains unanswered. Nevertheless, perioperative hypothermia had no sustained effect on LV function, either globally or regionally. Likewise, perioperative hypothermia was not associated with an increase in myocardial enzyme release. In fact, the data suggests that perioperative hypothermia might actually have had a very small *beneficial* effect in this regard. This is consistent with some animal studies that indicate mild systemic hypothermia (34°C) may decrease myocardial infarct size.[54] To date, however, human clinical trials of mild systemic hypothermia in the setting of acute myocardial infarction have not consistently shown evidence of benefit.[55,56]

Limitations

The findings and conclusions of this study should be considered with the following limitations in mind. This report is one of several *post hoc* ancillary analyses of the IHAST dataset,[28, 57-62] although there is no overlap between this study and prior IHAST *post hoc* analyses. A fundamental weakness of any *post hoc* analyses is that it typically asks questions for which the primary study was not designed. As such, *post hoc* analyses should be considered as a method of hypothesis generation rather than hypothesis testing. However, IHAST data collection was specifically designed to monitor and compare the occurrence of pre-defined cardiovascular events between hypothermic and normothermic patients. This strength is offset by several potential weaknesses.

One weakness is that many cardiovascular events occurred at very low rates. As a result, despite a large number of patients (1,000) the statistical power to detect a difference between temperature groups was low for many events (*e.g.*, myocardial infarction). In an attempt to address this weakness, we developed several composite cardiovascular outcome measures. None of these composite outcomes differed between temperature groups and, in all cases odds, ratios were very close to 1.00, indicating no increased risk with hypothermia. For example, for “any cardiovascular event—postoperative,” the upper confidence bound for the odds ratio is 1.17. This means that there is a very high probability that hypothermia increased the number of IHAST patients who experienced postoperative cardiovascular events *by no more than 17%* of the normothermic rate. With 42% of normothermic patients experiencing a postoperative cardiovascular event, this means that, *at most*, hypothermia might increase cardiovascular events by (17% × 42%) 7% (absolute value) over that occurring with normothermia. Nevertheless, for many of the other composite outcomes, the odds ratio confidence intervals remained sufficiently wide as to not preclude the possibility of a Type II error. While we observed no indication that perioperative hypothermia increased the incidence cardiovascular events, we wish to reemphasize that this observation must be considered to apply only to patients who have a low preoperative risk of CAD.

Another weakness of this *post hoc* analysis is that it has limited capacity to determine the extent to which cardiovascular events may have affected outcome. While cardiovascular events contributed only slightly to mortality (one patient directly, four patients indirectly), the indirect effect of cardiovascular events on 3-month functional status is less certain. The majority of cardiovascular events were, in fact interventions intended to support cerebral perfusion—most commonly to prevent or treat intraoperative hypotension and/or postoperative symptomatic cerebral vasospasm. Thus, many cardiovascular events likely reflect a *response* to a clinical event rather than being primary (causative) adverse events. Nevertheless, it is possible that some cardiovascular events may have had a direct effect on net neurological recovery and functional status.

Finally, although cardiovascular events were followed prospectively, events were detected as part of routine clinical care. Except for MIDS patients, protocol-driven serial postoperative assessments of cardiovascular status were not utilized. As a consequence, the observed rates of cardiovascular events—in particular, postoperative myocardial infarction and arrhythmias—are almost certainly less than if routine serial testing been used.

Conclusion

In summary, the results of IHAST and IHAST-MIDS indicate perioperative hypothermia was not associated with increased occurrence of cardiovascular events in good grade cerebral aneurysm surgery patients.

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References

1. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008;371:1955–69. [PubMed: 18539227]
2. Frank SM, Beattie C, Christopherson R, Norris EJ, Perler BA, Williams GM, Gottlieb SO. Unintentional hypothermia is associated with postoperative myocardial ischemia. Anesthesiology 1993;78:468–76. [PubMed: 8457047]
3. Bush HL Jr, Hydo LJ, Fischer E, Fantini GA, Silane MF, Barie PS. Hypothermia during elective abdominal aneurysm repair: The high price of avoidable morbidity. J Vasc Surg 1995;21:392–402. [PubMed: 7877221]
4. Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KR, Kelly S, Beattie C. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. JAMA 1997;277:1127–34. [PubMed: 9087467]
5. Todd MM, Hindman BJ, Clarke WR, Torner JC, IHAST Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005;352:135–45. [PubMed: 15647576]
6. Zaroff JG, Pawlikowska L, Miss JC, Yarlagadda S, Ha C, Achrol A, Kwok PY, McCulloch CE, Lawton MT, Ko N, Smith W, Young WL. Adrenoceptor polymorphisms and the risk of cardiac injury and dysfunction after subarachnoid hemorrhage. Stroke 2006;37:1680–5. [PubMed: 16728691]
7. Lee VH, Oh JK, Mulvagh SL, Wijdicks EF. Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2006;5:243–9. [PubMed: 17290097]
8. Samuels MA. The brain-heart connection. Circulation 2007;116:77–84. [PubMed: 17606855]
9. Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzmann JV, Raff H, Beattie C. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. Anesthesiology 1995;82:83–93. [PubMed: 7832339]
10. Drake CG. Report of World Federation of Neurological Surgeons committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988;68:985–6. [PubMed: 3131498]
11. Hindman BJ, Todd MM, Gelb AW, Loftus CM, Craen RA, Schubert A, Mahla ME, Torner JC. Mild hypothermia as a protective therapy during intracranial aneurysm surgery: A randomized prospective pilot trial. Neurosurgery 1999;44:23–33. [PubMed: 9894960]
12. Godet G, Gossens S, Prayssac P, Daghfous M, Delbrouck D, Aigret D, Coriat P. Infusion of propofol, sufentanil, or midazolam for sedation after aortic surgery: Comparison of oxygen consumption and hemodynamic stability. Anesth Analg 1998;87:272–6. [PubMed: 9706915]
13. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 1980;6:1–9. [PubMed: 7354892]
14. Wityk RJ, Pessin MS, Kaplan RF, Caplan LR. Serial assessment of acute stroke using the NIH Stroke Scale. Stroke 1994;25:362–5. [PubMed: 8303746]
15. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Eng J Med 1996;334:1209–15.
16. Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet 1996;347:289–92. [PubMed: 8569362]
17. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67. [PubMed: 2698218]

18. Bacher A, Illievich UM, Fitzgerald R, Ihra G, Spiss CK. Changes in oxygenation variables during progressive hypothermia in anesthetized patients. J Neurosurg Anesthesiol 1997;9:205–10. [PubMed: 9239580]
19. Kuwagata Y, Oda J, Ninomiya N, Shiozaki T, Shimazu T, Sugimoto H. Changes in left ventricular performance in patients with severe head injury during and after mild hypothermia. J Trauma 1999;47:666–72. [PubMed: 10528600]
20. Hicks CE, McCord MC, Blount SG Jr. Electrocardiographic changes during hypothermia and circulatory occlusion. Circulation 1956;13:21–8. [PubMed: 13277088]
21. Gunton RW, Scott JW, Lougheed WM, Botterell EH. Changes in cardiac rhythm and in the form of the electrocardiogram resulting from induced hypothermia in man. Am Heart J 1956;52:419–29. [PubMed: 13354603]
22. Fleming PR, Muir FH. Electrocardiographic changes in induced hypothermia in man. Br Heart J 1957;19:59–66. [PubMed: 13396078]
23. Emslie-Smith D, Sladden GE, Stirling GR. The significance of changes in the electrocardiogram in hypothermia. Br Heart J 1959;21:343–51. [PubMed: 13820224]
24. Schwab RH, Lewis DW, Killough JH, Templeton JY III. Electrocardiographic changes occurring in rapidly induced deep hypothermia. Am J Med Sci 1964;248:290–303. [PubMed: 14210305]
25. Okada M. The cardiac rhythm in accidental hypothermia. Electrocardiol 1984;17:123–8.
26. Lai YC, Manninen PH. Anesthesia for cerebral aneurysms: A comparison between interventional neuroradiology and surgery. Can J Anesth 2001;48:391–5. [PubMed: 11339784]
27. Fellahi JL, Parienti JJ, Hanouz JL, Plaud B, Riou B, Ouattara A. Perioperative use of dobutamine in cardiac surgery and adverse cardiac outcome. Propensity-adjusted analyses. Anesthesiology 2008;108:979–87. [PubMed: 18497597]
28. Hindman BJ, Bayman EO, Pfisterer WF, Torner JC, Todd MM, IHAST Investigators. No Association between intraoperative hypothermia or supplemental protective drug and neurological outcomes in patients undergoing temporary clipping during cerebral aneurysm surgery. Findings from the Intraoperative Hypothermia for Aneurysm Surgery Trial. Anesthesiology 2010;112:86–101. [PubMed: 19952722]
29. Solenski NJ, Haley EC Jr, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC. Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Crit Care Med 1995;23:1007–17. [PubMed: 7774210]
30. Kim DH, Haney CL, Van Ginhoven G. Reduction of pulmonary edema after SAH with a pulmonary artery catheter-guided hemodynamic management protocol. Neurocrit Care 2005;3:11–5. [PubMed: 16159089]
31. Frank SM, Cattaneo CG, Wieneke-Brady MB, El-Rahmany H, Gupta N, Lima JAC, Goldstein DS. Threshold for adrenomedullary activation and increased cardiac work during mild core hypothermia. Clin Sci 2002;102:119–25. [PubMed: 11749669]
32. Frank SM, Satitpunwaycha P, Bruce SR, Herscovitch P, Goldstein DS. Increased myocardial perfusion and sympathoadrenal activation during mild core hypothermia in awake humans. Clin Sci 2003;104:503–8. [PubMed: 12540290]
33. Mudge GH, Grossman W, Mills RM, Lesch M, Braunwald E. Reflex increase in coronary vascular resistance in patients with ischemic heart disease. N Engl J Med 1976;295:1333–7. [PubMed: 10527]
34. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. Circulation 1988;77:43–52. [PubMed: 2826047]
35. Breslow MJ, Parker SD, Frank SM, Norris EJ, Yates H, Raff H, Rock P, Christopherson R, Brosenfeld BA, Beattie C. Determinants of catecholamine and cortisol responses to lower extremity revascularization. Anesthesiology 1993;79:1202–9. [PubMed: 8267195]
36. Reynolds K, Beckmann J, Kurz A. Perioperative complications of hypothermia. Best Practice Res Clin Anaesthesiol 2008;22:645–57.
37. van der Bilt IAC, Hasan D, Vandertop WP, Wilde AAM, Algra A, Visser FC, Rinkel GJE. Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage. A meta-analysis Neurology 2009;72:635–42.

38. Mayer SA, Lin J, Homa S, Solomon RA, Hennihan L, Sherman D, Fink ME, Beckford A, Klebanoff LM. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. Stroke 1999;30:780–6. [PubMed: 10187879]
39. Yarlagadda S, Rajendran P, Miss JC, Banki NM, Kopelnik A, Wu AHB, Ko N, Gelb AW, Lawton MT, Smith WS, Young WL, Zaroff JG. Cardiovascular predictors of in-patient mortality after subarachnoid hemorrhage. Neurocrit Care 2006;5:102–7. [PubMed: 17099255]
40. Burch GE, Sun SC, Colcolough HL, DePasquale NP, Sohal RS. Acute myocardial lesions following experimentally-induced intracranial hemorrhage in mice: A histological and histochemical study. Arch Path 1967;84:517–21. [PubMed: 6054616]
41. Greenhoot JH, Reichenbach DD. Cardiac injury and subarachnoid hemorrhage. A clinical, pathological, and physiological correlation. J Neurosurg 1969;30:521–31. [PubMed: 5782382]
42. McNair JL, Clower BR, Sanford RA. The effect of reserpine pretreatment on myocardial damage associated with simulated intracranial hemorrhage in mice. Eur J Pharmacol 1970;9:1–6. [PubMed: 5434290]
43. Karch SB, Billingham ME. Myocardial contraction bands revisited. Human Pathol 1986;17:9–13. [PubMed: 2417934]
44. Doshi R, Neil-Dwyer G. A clinicopathological study of patients following a subarachnoid hemorrhage. J Neurosurg 1980;52:295–301. [PubMed: 7359184]
45. Elrifai AM, Bailes JE, Shih SR, Dianzumba S, Brillman J. Characterization of the cardiac effects of acute subarachnoid hemorrhage in dogs. Stroke 1996;27:737–42. [PubMed: 8614940]
46. Zaroff JG, Rordorf GA, Titus JS, Newell JB, Nowak NJ, Torchiana DF, Aretz HT, Picard MH. Regional myocardial perfusion after experimental subarachnoid hemorrhage. Stroke 2000;31:1136–43. [PubMed: 10797178]
47. Neil-Dwyer G, Walter P, Cruickshank JM, Doshi B, O'Groman P. Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid haemorrhage. Br Med J 1978;2:990–2. [PubMed: 361155]
48. Hunt D, Gore I. Myocardial lesions following experimental intracranial hemorrhage: Prevention with propranolol. Am Heart J 1972;83:232–6. [PubMed: 5058310]
49. Neil-Dwyer G, Cruickshank J, Stratton C. ß-blockers, plasma total creatine kinase and creatine kinase myocardial isoenzyme, and the prognosis of subarachnoid hemorrhage. Surg Neurol 1986;25:163–8. [PubMed: 2867610]
50. Walter P, Neil-Dwyer G, Cruickshank JM. Beneficial effects of adrenergic blockade in patients with subarachnoid haemorrhage. Br Med J 1982;284:1661–4. [PubMed: 6805647]
51. Neil-Dwyer G, Walter P, Cruickshank JM. ß-blockade benefits patients following a subarachnoid haemorrhage. Eur J Clin Pharmacol 1985;28(Suppl):25–9. [PubMed: 2865145]
52. Tung P, Kopelnik A, Banki N, Ong K, Ko N, Lawton MT, Gress D, Drew B, Foster E, Parmley W, Zaroff J. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. Stroke 2004;35:548–51. [PubMed: 14739408]
53. Kothavale A, Banki NM, Kopelnik A, Yarlagadda S, Lawton MT, Ko N, Smith WS, Drew B, Foster E, Zaroff JG. Predictors of left ventricular regional wall motion abnormalities after subarachnoid hemorrhage. Neurocrit Care 2006;4:199–205. [PubMed: 16757824]
54. Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. Am J Physiol (Heart Circ Physiol) 2002;282:H1584–91. [PubMed: 11959619]
55. O'Neill WW, Dixon SR. The year in interventional cardiology. J Am Coll Cardiol 2004;43:875–90. [PubMed: 14998632]
56. O'Neill WW, Dixon SR, Grines CL. The year in interventional cardiology. J Am Coll Cardiol 2005;45:1117–34. [PubMed: 15808773]
57. Leira EC, Davis PH, Martin CO, Torner JC, Yoo B, Weeks JB, Hindman BJ, Todd MM, IHAST Investigators. Improving prediction of outcome in “good grade” subarachnoid hemorrhage. Neurosurgery 2007;61:470–4. [PubMed: 17881957]
58. McGregor DG, Lanier WL, Pasternack JJ, Rusy DA, Hogan K, Samra S, Hindman B, Todd MM, Schroeder DR, Bayman EO, Clarke W, Torner J, Weeks J, IHAST Investigators. Effect of nitrous

oxide on neurological and neuropsychological function following intracranial aneurysm surgery. Anesthesiology 2008;108:568–79. [PubMed: 18362587]

59. Pasternak JJ, McGregor DG, Schroeder DR, Lanier WL, Shi Q, Hindman BJ, Clarke WR, Torner JC, Weeks J, Todd MM, IHAST Investigators. Hyperglycemia in patients undergoing cerebral aneurysm surgery: Its association with long-term gross neurologic and neuropsychological function. Mayo Clin Proc 2008;83:406–17. [PubMed: 18380986]
60. Coghlan LA, Hindman BJ, Bayman EO, Banki NM, Gelb AW, Todd MM, Zaroff JG, IHAST Investigators. Independent associations between electrocardiographic abnormalities and outcomes in patients with aneurysmal subarachnoid hemorrhage: Findings from the Intraoperative Hypothermia Aneurysm Surgery Trial. Stroke 2009;40:412–18. [PubMed: 19095990]
61. Pasternack JJ, McGregor DG, Lanier WL, Schroeder DR, Rusy DA, Hindman B, Clarke WR, Torner JC, Weeks J, Todd MM, IHAST Investigators. Effect of nitrous oxide use on long term neurologic and neuropsychological outcome in patients who received temporary proximal artery occlusion during cerebral aneurysm clipping surgery. Anesthesiology 2009;110:563–73. [PubMed: 19212259]
62. Todd MM, Hindman BJ, Clarke WR, Torner JC, Weeks JB, Bayman EO, Shi Q, Spofford CM, IHAST Investigators. Perioperative fever and outcome in surgical patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2009;64:897–908. [PubMed: 19404150]

Table 1

Patient Characteristics, Temperatures, and Intubation Status

	Temperature Group		
Characteristic	**Hypothermia (499)**	**Normothermia (501)**	***P*-Value**
Age, years	52 ± 12	51 ± 13	0.22
Female, n (%)	325 (65%)	330 (66%)	0.84
Current or Former Smoker, n (%)	309 (62%)	332 (66%)	0.17
History of Hypertension, n (%)	199 (40%)	199 (40%)	1.00
History of Coronary Artery Disease, n (%)	35 (7%)	18 (4%)	0.017
History of Ventricular Dysfunction, n (%)	2 (< 1%)	3 (1%)	1.00
History of Valvular Dysfunction, n (%)	5 (1%)	4 (1%)	0.75
History of Dysrhythmia, n (%)	13 (3%)	10 (2%)	0.54
Preoperative WFNS Score, n (%)			0.81
I	332 (67%)	328 (66%)	
II	140 (28%)	149 (30%)	
III	27 (5%)	24 (5%)	
Preoperative Fisher Score, n (%)			0.81
1	30 (6%)	24 (5%)	
2	172 (35%)	170 (34%)	
3	235 (47%)	239 (48%)	
4	62 (12%)	68 (14%)	
Aneurysm Size, mm, n (%)[a]			0.07
1 - 11	403 (81%)	401 (80%)	
12 - 24	85 (17%)	79 (16%)	
> 25	8 (2%)	20 (4%)	
Aneurysm Location, n (%)[b]			0.91
Anterior	458 (92%)	457 (91%)	
Posterior	41 (8%)	43 (9%)	
Temperature on Arrival to Operating Room, °C	36.8 ± 0.7	36.8 ± 0.6	0.91
Temperature at 1st Aneurysm Clip, °C	33.3 ± 0.8	36.7 ± 0.5	< 0.001
Temperature at End of Surgery, °C	34.2 ± 0.9	36.8 ± 0.6	< 0.001
Intubated at End of Surgery, n (%)	297 (60%)	122 (24%)	< 0.001

	Temperature Group		
Characteristic	**Hypothermia (499)**	**Normothermia (501)**	***P*-Value**
Temperature 2 h after Surgery, °C	36.4 ± 1.0	37.1 ± 0.7	< 0.001
Intubated 2 h after Surgery, n (%)	125 (25%)	66 (13%)	< 0.001
Intubated 24 h after Surgery, n (%)	48 (10%)	51 (10%)	0.83

Data are expressed as mean ± SD, or number (percentage).

[a] Four patients with missing data for aneurysm size; hypothermia (n = 3), normothermia (n = 1)

[b] One normothermic patient with missing data for aneurysm location. Anterior Aneurysms were defined as those involving the carotid, ophthalmic, anterior choroidal, middle cerebral, anterior communicating, posterior communicating, and anterior cerebral arteries. Posterior aneurysms included those involving the vertebrobasilar and posterior inferior cerebellar arteries.

WFNS = World Federation of Neurological Surgeons

Table 2

Cardiovascular Events or Procedures

		Temperature Group		
Event or Procedure	**Period[a]**	**Hypothermia (499)**	**Normothermia (501)**	**P Value**
Hypertension, not intended	Perioperative	32 (6%)	33 (7%)	1.00
	Postoperative	47 (9%)	41 (8%)	0.51
Hypertension, intended	Perioperative	14 (3%)	11 (2%)	0.55
	Postoperative	24 (5%)	23 (5%)	0.88
Hypotension, not intended	Perioperative	19 (4%)	18 (4%)	0.87
	Postoperative	18 (4%)	14 (4%)	0.48
Hypotension, intended	Perioperative	20 (4%)	26 (5%)	0.45
	Postoperative	1 (<1%)	0 (0%)	1.00[b]
Vasopressor, systemic[c]	Perioperative	44 (9%)	41 (8%)	0.74
	Postoperative	24 (5%)	16 (3%)	0.20
Vasopressor, cerebral	Perioperative	101 (20%)	91 (18%)	0.42
	Postoperative	95 (19%)	89 (18%)	0.63
Vasopressor, other	Perioperative	0 (0%)	0 (0%)	1.00[b]
	Postoperative	1 (< 1%)	2(<1%)	1.00
Myocardial ischemia or Infarction[c]	Perioperative	0 (0%)	1 (< 1%)[d]	1.00
	Postoperative	9 (2%)	4 (1%)	0.18
Congestive heart failure or pulmonary edema	Perioperative	10 (2%)	13 (3%)	0.67
	Postoperative	44 (9%)	50 (10%)	0.59
Cardiogenic shock[c]	Perioperative	0 (0%)	1 (< 1%)[d]	1.00
	Postoperative	0 (0%)	0 (0%)	1.00
Nonventricular arrhythmia[e]	Perioperative	25 (5%)	23 (5%)	0.77
	Postoperative	27 (5%)	34 (7%)	0.43
Ventricular-fibrillation or –tachycardia[c]	Perioperative	0 (0%)	1 (<1%)[d]	1.00
	Postoperative	6 (1%)	2 (<1%)	0.18
Other significant cardiovascular disorder or complication	Perioperative	0 (0%)	0 (0%)	1.00[b]
	Postoperative	8 (2%)	13 (3%)	0.38
Cardioversion or defibrillation	Perioperative	0 (0%)	2 (<1%)[d]	0.50
	Postoperative	2 (< 1%)	3 (< 1%)	1.00
Cardiac pacemaker placement	Perioperative	0 (0%)	1 (< 1%)	1.00
	Postoperative	0 (0%)	1 (< 1%)	1.00
Cardiopulmonary resuscitation[c]	Perioperative	1 (< 1%)[f]	1 (< 1%)[d]	1.00[b]
	Postoperative	7 (1%)	2 (< 1%)	0.11
Coronary angiogram[c]	Perioperative	0 (0%)	0 (0%)	1.00[b]
	Postoperative	1 (< 1%)	1 (< 1%)	1.00

		Temperature Group		
Event or Procedure	**Period[a]**	**Hypothermia (499)**	**Normothermia (501)**	**P Value**
Coronary angioplasty and/or stenting[c]	Perioperative	0 (0%)	0 (0%)	1.00[b]
	Postoperative	1 (< 1%)	0 (0%)	0.50
Cardiac surgery[c]	Perioperative	0 (0%)	0 (0%)	1.00[b]
	Postoperative	0 (0%)	0 (0%)	1.00[b]
Vascular surgery	Perioperative	0 (0%)	0 (0%)	1.00[b]
	Postoperative	0 (0%)	2 (< 1%)	0.50
Other cardiovascular procedure, intervention, or surgery	Perioperative	1 (< 1%)	0 (0%)	0.50
	Postoperative	36 (7%)	34 (7%)	0.81

All P values calculated using Fisher's Exact test.

[a] Perioperative events had their onset during surgery or during the first two hours after surgery. Postoperative events had their onset more than two hours after surgery until final 3-month follow-up.

[b] Default *P* value of 1.00 assigned because occurrence of event or procedure too low to satisfy assumptions of Fisher's Exact Test.

[c] "Indicator" event, see Methods for definition.

[d] In the perioperative period, one patient had intraoperative cardiac arrest and death, see Results for details.

[e] All arrhythmias that were not ventricular tachycardia or ventricular fibrillation, including sinus bradycardia.

[f] In the perioperative period, one patient had transient bradycardia/asystole in postoperative care area that responded to pharmacologic treatment.

Table 3

Composite Cardiovascular Events and Mortality

		Temperature Group			
Event or Procedure	**Period[a]**	**Hypothermia (499)**	**Normothermia (501)**	***P* Value**	**Odds Ratio (95% Confidence Interval)**
Any Cardiovascular Event	Perioperative	188 (38%)	164 (33%)	0.11	1.24 (0.96 - 1.61)
	Postoperative	196 (39%)	208 (42%)	0.48	0.91 (0.71 - 1.17)
Any Vasopressor Administration	Perioperative	132 (26%)	118 (24%)	0.31	1.17 (0.88 - 1.55)
	Postoperative	116 (23%)	105 (21%)	0.40	1.14 (0.85 - 1.54)
Any “Indicator” Cardiovascular Event	Perioperative	44 (9%)	42 (8%)	0.82	1.06 (0.68 - 1.64)
	Postoperative	31 (6%)	23 (5%)	0.27	1.38 (0.79 - 2.30)
Any Cardiovascular Event	Perioperative[b]	8 (2%)	6 (1%)	0.60	1.34 (0.46 - 3.90)
Rated Severe or Fatal	Postoperative[c]	24 (5%)	37 (7%)	0.11	0.64 (0.37 - 1.08)
Myocardial Infarction, Congestive Heart Failure or Pulmonary Edema, Ventricular Arrhythmia, Cardioversion or Defibrillation	Either Perioperative or Postoperative	62 (12%)	64 (13%)	0.92	0.97 (0.67 - 1.41)
Mortality (any cause)	Either Perioperative or Postoperative[c]	29 (6%)	32 (6%)	0.79	0.90 (0.54 - 1.52)

All P values calculated using Fisher's Exact test.

All odds ratios calculated with normothermia as the reference group.

[a] Perioperative events had their onset during surgery or during the first 2 h after surgery. Postoperative events had their onset more than 2 h after surgery until final 3-month follow-up.

[b] In the perioperative period, one patient had intraoperative cardiac arrest and death, see Results for details. In the perioperative period the most common events rated as severe (but nonfatal) were vasopressor, systemic (n = 7), hypertension, not intended (n = 4), and vasopressor, cerebral (n = 2).

[c] See Results regarding postoperative deaths.

Table 4

Myocardial Injury and Dysfunction Sub-Study—Left Ventricular Performance and Cardiac Troponin I

Variables	Temperature Group		*P* Value
	Hypothermia (n = 33)	Normothermia (n = 29)	
Left Ventricular Ejection Fraction			
Preoperative[a]	0.69 (0.64, 0.75) (n = 30)	0.64 (0.62, 0.73) (n = 24)	0.16
Postoperative[b]	0.72 (0.63, 0.75) (n = 28)	0.69 (0.62, 0.73) (n = 22)	
Postoperative *vs.* Preoperative Change	-0.01 (-0.06, 0.07) (n = 26)	0.01 (-0.03, 0.06) (n = 20)	0.51
Regional Wall Motion Score			
Preoperative[c]	1.00 (1.00, 1.00) (n = 32)	1.00 (1.00, 1.00) (n = 29)	0.62
Postoperative	1.00 (1.00, 1.00) (n = 33)	1.00 (1.00, 1.00) (n = 29)	
Postoperative *vs.* Preoperative Change[d]	0.00 (0.00, 0.00) (n = 32)	0.00 (0.00, 0.00) (n = 29)	0.61
Cardiac Troponin I (mcg/L)			
Preoperative[e]	0.03 (0.03, 0.04) (n = 26)	0.03 (0.03, 0.03) (n = 25)	0.43
Postoperative[f]	0.03 (0.03, 0.04) (n = 26)	0.03 (0.03, 0.04) (n = 24)	
Postoperative *vs.* Preoperative Change[g]	0.00 (-0.01, 0.00) (n = 26)	0.01 (-0.03, 0.06) (n = 24)	0.038

Values are reported as median, (25^{th} and 75^{th} quartile values).

All *P*-values are calculated using Wilcoxon Rank Sum test.

[a] Any preoperative left ventricular ejection fraction < 50%: Hypothermia = 1/30, Normothermia = 0/24.

[b] Any postoperative left ventricular ejection fraction < 50%: Hypothermia = 0/28, Normothermia = 1/22.

[c] Any preoperative wall motion score > 1.00: Hypothermia = 2/32, Normothermia = 1/29.

[d] Any postoperative increase (worsening) of wall motion score: Hypothermia = 2/32, Normothermia = 2/29.

[e] Any preoperative troponin > 1 mcg/L: Hypothermia = 1/26, Normothermia = 0/25.

[f] Any postoperative troponin > 1 mcg/L: Hypothermia = 0/26, Normothermia = 2/24.

[g] Any postoperative troponin increase: Hypothermia = 3/26, Normothermia = 5/24.