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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

Hoang P. Nguyen, M.D.,* Jonathan G. Zaroff, M.D.,† Emine O. Bayman, Ph.D.,‡ Adrian W. Gelb, M.B., Ch.B.,§ Michael M. Todd, M.D.,‖ Bradley J. Hindman, M.D.#; on behalf of the IHAST-MIDS and IHAST Investigators**

ABSTRACT

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

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, and others) were prospectively followed until 3-month follow-up and were compared in 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 postoperative *versus* 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.

* Resident, Department of Medicine, Kaiser San Francisco Medical Center, San Francisco, California. † Adjunct Investigator, Kaiser Northern California Division of Research, San Francisco, California. ‡ Associate, Department of Anesthesia, Roy J. and Lucille A. Carver College of Medicine, and Department of Biostatistics, College of Public Health, The University of Iowa, Iowa City, Iowa. § Professor of Clinical Anesthesia, Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California. ‖ Professor and Head, # Professor and Vice-Chair (Faculty Development), Department of Anesthesia, Roy J. and Lucille A. Carver College of Medicine, The University of Iowa. ** Members of the IHAST-MIDS and IHAST Study are listed in appendix 1.

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Address correspondence to Dr. Hindman: Department of Anesthesia, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242. brad-hindman@uiowa.edu.

What We Already Know about This Topic

- Perioperative hypothermia has been associated with postoperative cardiovascular complications, including cardiac injury and dysfunction

What This Article Tells Us That Is New

- In 1,000 patients randomized to normothermia or mild (33°C) hypothermia during craniotomy, patients were rewarmed before endotracheal extubation, even if this required ventilation in the postanesthesia recovery area for 2 hr
- Under these circumstances, intraoperative and very early postoperative hypothermia was not associated with an increase in adverse cardiovascular events

THERE is a 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 neurologic benefits of hypothermia are several known or potential risks. For example, in the perioperative period, mild systemic hypothermia has been reported to increase the occurrence of various cardiovascular events 2- to 6-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 neurologic outcome in patients undergoing surgery to treat acutely ruptured intracranial aneurysms when compared with intraoperative normothermia.[5] As a part of trial safety monitoring, IHAST prospectively followed events in other organ systems, including the cardiovascular system. The aim of the current study was 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 dysfunction, such as positive myocardial enzymes, regional wall motion abnormalities, and left ventricular (LV) dysfunction.[6] These abnormalities seem 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 preoperative and postoperative assessments of myocardial injury (cardiac troponin-I [cTnI]) and LV function (echocardiography).

Materials and Methods

The 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 Neurologic 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 determined similarly. 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 the surgery. IHAST protocols recommended that patients who were still hypothermic (below 35.5°C) at the end of the 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 after the end of surgery.

IHAST Data Collection and Safety Monitoring

All IHAST data collection, preoperative and postoperative management decisions, and outcome assessments were made by persons 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 and 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 before the 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 (IEs). IEs were categorized as occurring in one of nine body systems: (1) whole body or general, (2) cardiovascular, (3) respiratory, (4) digestive, (5) endocrine or metabolic, (6) neurologic or neurosurgical, (7) urogenital, (8) coagulation or hematologic, and (9) other or unclassified. Across all nine IE categories, a total of 68 specific events and 38 procedures or interventions were followed. Each IE had predefined 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 were classified by local investigators as (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 the duration of hospitalization was slightly prolonged. Severe events were life threatening, permanently disabling, or substantively prolonged in-patient hospitalization. IEs with a rating of death were those that resulted in patient death.

A predefined subset of IEs (n = 27) were designated as "indicator" IEs. Indicator IEs were events that previous 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 events associated with major neurologic morbidity (*e.g.*, intracranial hemorrhage, intracranial hypertension, brain swelling, and 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 1 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 that diagnostic criteria were met and that all associated IEs 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 the 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-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 IEs are summarized in appendix 2. Eight of the 26 cardiovascular events (*e.g.*, myocardial infarction, ventricular arrhythmias, and vasopressors to support the systemic circulation) were also designated as indicator IEs. Because both hypotension and hypertension can be deliberately used 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), neurologic 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 absolute increases of 6.5 and 5% and relative increases of 1.65 and 2.00 in hypothermic patients, respectively.

Myocardial Injury and Dysfunction Sub-study

With the approval of the IHAST Data and Safety Monitoring Board, in December 2000, 12 IHAST centers were invited to participate in a supplementary exploratory study, the Myocardial Injury and Dysfunction Sub-Study (MIDS). Seven centers accepted (appendix 1), and in these centers, informed consent documents included additional information regarding MIDS procedures. The aim of MIDS was to determine whether perioperative hypothermia was associated with increases in troponin release, LV dysfunction, or regional wall motion abnormalities.

Patients enrolled in MIDS (n = 62) underwent preoperative and postoperative blood collection and transthoracic echocardiography (TTE). Preoperative TTE and serum collection were obtained not more than 24 h before

surgery, and both procedures were repeated within 8–24 h after surgery. TTE system settings were chosen to maximize the 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 (midpapillary level), apical four-chamber, apical two-chamber, and apical three-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 examination relative to surgery, and all other clinical information. All coded TEE studies were interpreted by a single experienced echocardiographer (J.Z.). LV 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 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 preoperatively 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 cTnI were measured (Beckman Coulter Access 2, Chemiluminescence Immunoassay; Beckman Coulter Canada Inc., Mississauga, ON, 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 that 25% of patients with SAH would have at least some preoperative wall motion abnormalities (RWMS > 1.0 with SD of 0.3).[6] We assumed that only those patients with preoperative RWMS more than 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 version 9.1.3 Service Pack XP_PRO Platform (SAS Institute Inc., Cary, NC). Power analyses were performed using nQuery Advisor version 7.0 (Statistical Solutions Ltd., Cork, Ireland). All analyses were based on intention to treat. The univariate tests used included the Fisher 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 $P \leq 0.05$ as the threshold for a statistically significant difference or association without adjustment for multiple comparisons.

For the entire IHAST population (n = 1,000), preoperative and postoperative variables and the occurrence of cardiovascular events were compared in 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 the differences between temperature groups, cardiovascular events were grouped *post hoc* into various composite categories (*e.g.*, any cardiovascular event, any indicator event). For the calculation of composite cardiovascular events, 4 of the 26 cardiovascular IEs 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 that a cardiovascular event occurred. For all composite events, odds ratios and 95% CI were also calculated, using normothermia as the reference group.

For the MIDS population (n = 62), preoperative and postoperative values for cTnI, RWMS, and LVEF were compared in hypothermic and normothermic patients. In addition, using paired preoperative and postoperative values, the change in each of these variables was calculated and compared in hypothermic and normothermic patients. Because there is no established threshold 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 *versus* 4%, respectively, $P = 0.017$.

Table 1. Patient Characteristics, Temperatures, and Intubation Status

Characteristic	Temperature Group		*P* Value
	Hypothermia (n = 499)	Normothermia (n = 501)	
Age, yr	52 ± 12	51 ± 13	0.22
Female	325 (65)	330 (66)	0.84
Current or former smoker	309 (62)	332 (66)	0.17
History of hypertension	199 (40)	199 (40)	1.00
History of coronary artery disease	35 (7)	18 (4)	0.017
History of ventricular dysfunction	2 (< 1)	3 (1)	1.00
History of valvular dysfunction	5 (1)	4 (1)	0.75
History of dysrhythmia	13 (3)	10 (2)	0.54
Preoperative WFNS score			0.81
I	332 (67)	328 (66)	
II	140 (28)	149 (30)	
III	27 (5)	24 (5)	
Preoperative Fisher score			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*			0.07
1–11	403 (81)	401 (80)	
12–24	85 (17)	79 (16)	
>25	8 (2)	20 (4)	
Aneurysm location†			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 first 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	297 (60)	122 (24)	< 0.001
Temperature 2 h after surgery, °C	36.4 ± 1.0	37.1 ± 0.7	< 0.001
Intubated 2 h after surgery	125 (25)	66 (13)	< 0.001
Intubated 24 h after surgery	48 (10)	51 (10)	0.83

Data are expressed as mean ± SD or n (%).

* Four patients with missing data for aneurysm size; hypothermia (n = 3) and normothermia (n = 1). † 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.

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 the time of first aneurysm clipping. Although rewarming of hypothermic patients began after final clip placement, core temperatures increased by only approximately 1°C by the end of the surgery (34.2° ± 0.9°C). Consequently, 60% of those randomized to hypothermia remained intubated on arrival to the postoperative care area compared with 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 *versus* 13%, respectively, $P < 0.001$. At 24 h after surgery, intubation was equally common in both groups (i.e., approximately 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%), congestive heart failure or pulmonary edema (9%), 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 perioperative or the postoperative period. Likewise, as summarized in table 3, the number of patients who experienced any cardio-

Table 2. Cardiovascular Events or Procedures

Event or Procedure	Period*	Temperature Group: Hypothermia (n = 499)	Temperature Group: Normothermia (n = 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†
Vasopressor, systemic‡	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†
	Postoperative	1 (< 1)	2 (< 1)	1.00
Myocardial ischemia or infarction‡	Perioperative	0 (0)	1 (< 1)§	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‡	Perioperative	0 (0)	1 (< 1)§	1.00
	Postoperative	0 (0)	0 (0)	1.00
Nonventricular arrhythmia‖	Perioperative	25 (5)	23 (5)	0.77
	Postoperative	27 (5)	34 (7)	0.43
Ventricular fibrillation or ventricular tachycardia‡	Perioperative	0 (0)	1 (< 1)§	1.00
	Postoperative	6 (1)	2 (< 1)	0.18
Other significant cardiovascular disorder or complication	Perioperative	0 (0)	0 (0)	1.00†
	Postoperative	8 (2)	13 (3)	0.38
Cardioversion or defibrillation	Perioperative	0 (0)	2 (< 1)§	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‡	Perioperative	1 (< 1)#	1 (< 1)§	1.00†
	Postoperative	7 (1)	2 (< 1)	0.11
Coronary angiogram‡	Perioperative	0 (0)	0 (0)	1.00†
	Postoperative	1 (< 1)	1 (< 1)	1.00
Coronary angioplasty and stenting‡	Perioperative	0 (0)	0 (0)	1.00†
	Postoperative	1 (< 1)	0 (0)	0.50
Cardiac surgery‡	Perioperative	0 (0)	0 (0)	1.00†
	Postoperative	0 (0)	0 (0)	1.00†
Vascular surgery	Perioperative	0 (0)	0 (0)	1.00†
	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

Data are expressed as n (%). All *P* values calculated using Fisher exact test.

* Perioperative events had their onset during surgery or during the first 2 h after surgery. Postoperative events had their onset > 2 h after surgery until final 3-month follow-up. † Default *P* value of 1.00 assigned because the occurrence of event or procedure is too low to satisfy assumptions of Fisher exact test. ‡ "Indicator" event, see Materials and Methods for definition. § In the perioperative period, one patient had intraoperative cardiac arrest and death, see Results for details. ‖ All arrhythmias that were not ventricular tachycardia or ventricular fibrillation, including sinus bradycardia. # In the perioperative period, one patient had transient bradycardia or asystole in postoperative care area that responded to pharmacologic treatment.

vascular 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 in hypothermic and normothermic patients.

Sixty-one patients died between randomization and 3-month follow-up. The primary causes of death were neurologic in 46 patients (75%), respiratory in 6 (10%), pulmonary embolus in 4 (7%), sepsis in 4 (7%), and cardiovascular in 1 patient (less than 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

Table 3. Composite Cardiovascular Events and Mortality

Event or Procedure	Period*	Temperature Group: Hypothermia (n = 499)	Temperature Group: Normothermia (n = 501)	*P* Value	Odds Ratio (95% CI)
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†	8 (2)	6 (1)	0.60	1.34 (0.46–3.90)
Rated severe or fatal	Postoperative‡	24 (5)	37 (7)	0.11	0.64 (0.37–1.08)
Myocardial infarction, congestive heart failure or pulmonary edema, ventricular arrhythmia, and 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‡	29 (6)	32 (6)	0.79	0.90 (0.54–1.52)

Data are expressed as n (%). All *P* values calculated using Fisher exact test. All odds ratios calculated with normothermia as the reference group.

* 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. † 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). ‡ See Results regarding postoperative deaths.

ischemia and arrhythmia. Fourteen patients (hypothermia, n = 8; normothermia, n = 6) had 30 postoperative cardiovascular IEs rated by local investigators as fatal. However, none of these cardiovascular events was 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 neurologic 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 multisystem failure. One patient died from sepsis shortly after 3-month follow-up, for a total of 62 deaths in the trial.

MIDS Population

The preoperative 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 *versus* 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 in MIDS patients assigned to hypothermia (n = 33) and normothermia (n = 29), and the occurrence of cardiovascular events did not differ in 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, values for hypothermic MIDS patients exhibited no net change in cTnI in preoperative 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 the outcomes were prospectively assessed by the examiners unaware of intraoperative temperature using predefined diagnostic criteria. Perioperative hypothermia was not associated with an improved neurologic 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 con-

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*	0.69 (0.64, 0.75) (n = 30)	0.64 (0.62, 0.73) (n = 24)	0.16
Postoperative†	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‡	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§	0.00 (0.00, 0.00) (n = 32)	0.00 (0.00, 0.00) (n = 29)	0.61
Cardiac troponin I (μg/l)			
Preoperative‖	0.03 (0.03, 0.04) (n = 26)	0.03 (0.03, 0.03) (n = 25)	0.43
Postoperative#	0.03 (0.03, 0.04) (n = 26)	0.03 (0.03, 0.04) (n = 24)	
Postoperative *vs*. preoperative change**	0.00 (−0.01, 0.00) (n = 26)	0.01 (−0.03, 0.06) (n = 24)	0.038

Values are expressed as median (25th and 75th quartile values). All *P* values are calculated using Wilcoxon rank sum test.

* Any preoperative left ventricular ejection fraction < 50%: hypothermia = 1 of 30, normothermia = 0 of 24. † Any postoperative left ventricular ejection fraction < 50%: hypothermia = 0 of 28, normothermia = 1 of 22. ‡ Any preoperative wall motion score greater than 1.00: hypothermia = 2 of 32, normothermia = 1 of 29. § Any postoperative increase (worsening) of Wall Motion Score: hypothermia = 2 of 32, normothermia = 2 of 29. ‖ Any preoperative troponin > 1 μg/l: hypothermia = 1 of 26, normothermia = 0 of 25. # Any postoperative troponin greater than 1 μg/l: hypothermia = 0 of 26, normothermia = 2 of 24. ** Any postoperative troponin increase: hypothermia = 3 of 26, normothermia = 5 of 24.

sistent with studies showing that in anesthetized patients, systemic hemodynamics (*e.g.*, mean arterial pressure, systemic vascular resistance, and heart rate[18]) and LV performance (*e.g.*, cardiac index,[18] fractional shortening, and 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.*[26] in a series of 100 patients undergoing cerebral aneurysm surgery (29%). 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.*[27] reported that in patients undergoing cardiac surgery, perioperative vasopressor use (primarily dobutamine) was associated with less favorable outcome (ventricular arrhythmias, myocardial infarction, and death). 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 10 standard covariates (*e.g.*, age, preoperative WFNS class, aneurysm location, and Fisher score),[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 seemed to be related to the use of deliberate (intended) hypotension in a normothermic patient with unrecognized three-vessel CAD. Although previously a common practice, induced hypotension is now infrequently used in cerebral aneurysm surgery. In IHAST, deliberate intraoperative hypotension was used in 16 of 30 centers and in less than 5% of patients. In a multivariate model that included 10 standard covariates (*e.g.*, age, preoperative WFNS class, aneurysm location, Fisher score),[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 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. 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 cardiac output prevent or treat post-SAH cerebral vasospasm. Solenski *et al.*[29] reported that pulmonary edema occurred in 29% of postoperative SAH patients in whom intentional hypervolemia and induced hypertension were routinely employed. 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 aggressive hyperdynamic therapy in IHAST. Consistent with that hypothesis, Kim *et al.*[30] reported that pulmonary edema in postoperative SAH patients decreased from 14 to 6% when

less aggressive hypervolemic therapy was used. 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 or infarction (1%), ventricular arrhythmias (1%), and cardiogenic shock (0%) was low and did not differ in patients randomized to hypothermia and normothermia. Nearly identical rates for these three events were reported by Solenski *et al.*[29] in a group of 455 surgical SAH patients. 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 cited widely and have been used as evidence to support standards regarding maintenance of perioperative normothermia.††‡‡ Given the impact and influence of previous 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.*[2] reported a nonrandomized study of 100 patients undergoing lower extremity vascular surgery. Patients with unintentional hypothermia (recovery room temperatures below 35°C, n = 33) had, when compared with patients with temperatures at or above 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%) in hypothermic and normothermic patients. In 1995, Bush *et al.*[3] reported a nonrandomized study of 262 patients undergoing abdominal aortic aneurysm surgery. Patients with unintentional hypothermia (postoperative temperatures below 34.5°C, n = 66) had, when compared with patients with temperatures at or above 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.*[4] reported a randomized trial of intraoperative temperature management in 300 patients undergoing thoracic, abdominal, or vascular surgery. 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 most obvious differences between IHAST and previous reports are with regard to study design and patient characteristics. In two of the three previous studies, intraoperative 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.*,[3] patients who became hypothermic intraoperatively had larger aortic aneurysms, greater operative time, greater fluid requirements, greater blood loss, and greater transfusion requirements. 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 the patients in previous studies had a much greater incidence of CAD. In the 1997 study by Frank *et al.*,[4] 49% of their patients had known CAD compared with 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.*[4] observed that the occurrence of myocardial ischemia and ventricular arrhythmias was equivalent in hypothermic and normothermic patients. However, on emergence, hypothermic patients more commonly developed hypertension, probably in response to increased circulating catecholamines.[4] This hypothesis was based on their previous 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.*[31,32] 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%. 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.*[32] have shown that β-adrenergic receptor blockade decreases hypothermia-induced

†† 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. Available at: http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/Current+NHQM+Manual.htm. Accessed January 22, 2010.

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

systemic catecholamines and eliminates hyperdynamic cardiovascular responses.

Therefore, the collective evidence indicates that 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 that patients with CAD may also exhibit a pathologic increase in coronary vascular resistance in response to cold stimuli, perhaps because of impaired coronary artery endothelial function.[33,34] If so, it is possible that this response might also contribute to hypothermia's adverse cardiovascular effects in patients with CAD.

Because 95% of IHAST patients had no 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 in hypothermic and normothermic patients. Breslow *et al.*[35] showed that general anesthesia attenuates sympathetic activity and catecholamine responses to noxious stimuli. By maintaining sedation or 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 on 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 wound infection.[36] However, in patients with low 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 patients with SAH may have signs of acute myocardial injury and LV dysfunction[37] and that these abnormalities may independently contribute to less favorable outcomes.[38,39] In a study of 182 patients with SAH, Zaroff *et al.*[6] reported that LV regional wall motion abnormalities were present in 25% of patients, elevated troponin (cTnI greater than 1 μg/L) was present in 13%, and decreased LVEF (less than or equal to 50%) was present in 12%. The weight of current evidence supports the concept that SAH-associated cardiac injury is adrenergically mediated and triggered by pathologic release of catecholamines at cardiac sympathetic nerve terminals at the time of the initial SAH.[8] The result is a 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-adrenergic receptor blockers[48] and drugs that deplete norepinephrine stores.[42] Neil-Dwyer *et al.*[49] reported that patients with SAH randomized to receive β-adrenergic receptor blockers seemed to have decreased myocardial enzyme release 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 patients with SAH[6] in that it had an extremely low incidence of preoperative myocardial injury or dysfunction. In the MIDS population, preoperative regional wall motion abnormalities were present in only 5% (3 of 61 patients), increased preoperative troponin (cTnI greater than 1 μg/l) was present in 2% (1 of 51 patients), and preoperative LVEF less than 50% was present in only 2% (1 of 54 patients). These rates were 5- to 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 of 62) of patients were WFNS I or II. SAH-associated troponin release[52] and regional wall motion abnormalities[53] are both associated with poor neurologic grades (Hunt and Hess grades of 3 or more). Therefore, it seems that 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 suggest that perioperative hypothermia might actually have had a very small beneficial effect in this regard. This is consistent with some animal studies indicating that 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 previous 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 a method of hypothesis generation rather than hypothesis testing. However, IHAST data collection was specifically designed to monitor and compare the occurrence of predefined cardiovascular events

in 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 other composite outcomes, the odds ratio CIs remained sufficiently wide as to not preclude the possibility of a type II error. Although we observed no indication that perioperative hypothermia increased the incidence of 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. Although cardiovascular events contributed only slightly to mortality (one patient directly and 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 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 neurologic recovery and functional status.

Finally, although cardiovascular events were followed up prospectively, events were detected as a part of routine clinical care. Except for MIDS patients, protocol-driven serial postoperative assessments of cardiovascular status were not used. 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 that perioperative hypothermia was not associated with the increased occurrence of cardiovascular events in good grade cerebral aneurysm surgery patients.

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Appendix 1: IHAST and Myocardial Injury and Dysfunction Sub-study Members

IHAST Members

University of Iowa Steering Committee: M. Todd, B. Hindman, W. Clarke, K. Chaloner, J. Torner, P. Davis, M. Howard, D. Tranel, S. Anderson; Clinical Coordinating Center: M. Todd, B. Hindman, J. Weeks, L. Moss, J. Winn; Data Management Center: W. Clarke, K. Chaloner, M. Wichman, R. Peters, M. Hansen, D. Anderson, J. Lang, B. Yoo; Physician Safety Monitor: H. Adams; Project Advisory Committee: G. Clifton (University of Texas, Houston, Texas), A. Gelb (University of California, San Francisco, California), C. Loftus (Temple University, Philadelphia, Pennsylvania), A. Schubert (Cleveland Clinic, Cleveland, Ohio); Physician Protocol Monitor: D. Warner (Duke University, Durham, North Carolina); Data and Safety Monitoring Board: W. Young, Chair (University of California, San Francisco, California), R. Frankowski (University of Texas Health Science Center at Houston School of Public Health, Houston, Texas), K. Kieburtz (University of Rochester School of Medicine and Dentistry, Rochester, New York), D. Prough, (University of Texas Medical Branch, Galveston, Texas), L. Sternau (Mt. Sinai Medical Center, Miami, Florida); National Institutes of Health, National Institute of Neurologic Disorders and Stroke, Bethesda, Maryland: J. Marler, C. Moy, B. Radziszewska.

The Members of the Myocardial Injury and Dysfunction Sub-study

Steering Committee: B. Hindman (University of Iowa Health Care, Iowa City, Iowa), J. Zaroff (University of California, San Francisco, California), A. Gelb (University of California, San Francisco, California); Specimen Management and Analysis: R. Craen (University of Western Ontario, London, Ontario, Canada); L. Coghlan, (University of California, San Francisco, California).

Myocardial Injury and Dysfunction Sub-Study Participating Centers/Investigators (number of patients in parentheses) are as follows: Auckland City Hospital, Auckland, New Zealand (20): T. Short; Sozialmedizinisches Zentrum Ost–Donauspital, Vienna, Austria (17): R. Greif, R. Spinka; Alfred Hospital, Melbourne, Australia (10): P. Myles; University of California, San Francisco, California (7): L. Litt, M. Lawton; University of Iowa Health Care, Iowa City, Iowa (4): M. Maktabi; University of Michigan Medical Center, Ann Arbor, Michigan (3): S. Samra, B. Thompson; Harborview Medical Center, Seattle, Washington (1): A. Lam.

IHAST Participating Centers (the number of randomized patients at each center is listed in parentheses) are as follows: Addenbrooke's Hospital, Cambridge, United Kingdom (93): B. Matta, P. Kirkpatrick, D. Chatfield, C. Skilbeck, R. Kirollos, F. Rasulo, K. English, C. Duffy, K. Pedersen, N. Scurrah, R. Burnstein, A. Prabhu, C. Salmond, A. Blackwell, J. Birrell, S. Jackson; University of Virginia Health System, Charlottesville, Virginia (86): N. Kassell, T. Pajewski, H. Fraley, A. Morris, T. Alden, M. Shaffrey, D. Bogdonoff, M. Durieux, Z. Zuo, K. Littlewood, E. Nemergut, R. Bedford, D. Stone, P. Balestrieri, J. Mason, G. Henry, P. Ting, J. Shafer, T. Blount, L. Kim, A. James, E. Farace, L. Clark, M. Irons, T. Sasaki, K. Webb; Auckland City Hospital, Auckland, New Zealand (69): T. Short, E. Mee, J. Ormrod, J. Jane, T. Alden, P. Heppner, S. Olson, D. Ellegala, C. Lind, J. Sheehan, M. Woodfield, A. Law, M. Harrison, P. Davies, D. Campbell, N. Robertson, R. Fry, D. Sage, S. Laurent, C. Bradfield, K. Pedersen, K. Smith, Y. Young, C. Chambers, B. Hodkinson, J. Biddulph, L. Jensen, J. Ogden, Z. Thayer, F. Lee, S. Crump, J. Quaedackers, A. Wray, V. Roelfsema; Sozialmedizinisches Zentrum Ost–Donauspital, Vienna, Austria (58): R. Greif, G. Kleinpeter, C. Lothaller, E. Knosp, W. Pfisterer, R. Schatzer, C. Salem, W. Kutalek, E. Tuerkkan, L. Koller, T. Weber, A. Buchmann, C. Merhaut, M. Graf, B. Rapf; Harborview Medical Center, Seattle, Washington (58): A. Lam, D. Newell, P. Tanzi, L. Lee, K. Domino, M. Vavilala, J. Bramhall, M. Souter, G. Britz, H. Winn, H. Bybee; St. Vincent's Public Hospital, Melbourne, Australia (57): T. Costello, M. Murphy, K. Harris, C. Thien, D. Nye, T. Han, P. McNeill, B. O'Brien, J. Cormack, A. Wyss, R. Grauer, R. Popovic, S. Jones, R. Deam, G. Heard, R. Watson, L. Evered, F. Bardenhagen, C. Meade, J. Haartsen, J. Kruger, M. Wilson; University of Iowa Health Care, Iowa City, Iowa (56): M. Maktabi, V. Traynelis, A. McAllister, P. Leonard, B. Hindman, J. Brian, F. Mensink, R. From, D. Papworth, P. Schmid, D. Dehring, M. Howard, P. Hitchon, J. VanGilder, J. Weeks, L. Moss, K. Manzel, S. Anderson, R. Tack, D. Taggard, P. Lennarson, M. Menhusen; University of Western Ontario, London, Ontario, Canada (53): A. Gelb, S. Lownie, R. Craen, T. Novick, G. Ferguson, N. Duggal, J. Findlay, W. Ng, D. Cowie, N. Badner, I. Herrick, H. Smith, G. Heard, R. Peterson, J. Howell, L. Lindsey, L. Carriere, M. von Lewinski, B. Schaefer, D. Bisnaire, P. Doyle-Pettypiece, M. McTaggart; Keck School of Medicine at University of Southern California, Los Angeles, California (51): S. Giannotta, V. Zelman, E. Thomson, E. Babayan, C. McCleary, D. Fishback;

University of Michigan Medical Center, Ann Arbor, Michigan (41): S. Samra, B. Thompson, W. Chandler, J. Mcgillicuddy, K. Tremper, C. Turner, P. Smythe, E. Dy, S. Pai, V. Portman, J. Palmisano, D. Auer, M. Quigley, B. Giordani, A. Freymuth, P. Scott, R. Silbergleit, S. Hickenbottom; University of California, San Francisco, California (39): L. Litt, M. Lawton, L. Hannegan, D. Gupta, P. Bickler, B. Dodson, P. Talke, I. Rampil, B. Chen, P. Wright, J. Mitchell, S. Ryan, J. Walker, N. Quinnine, C. Applebury; Alfred Hospital, Melbourne, Australia (35): P. Myles, J. Rosenfeld, J. Hunt, S. Wallace, P. D'Urso, C. Thien, J. McMahon, S. Wadanamby, K. Siu, G. Malham, J. Laidlaw, S. Salerno, S. Alatakis, H. Madder, S. Cairo, A. Konstantatos, J. Smart, D. Lindholm, D. Bain, H. Machlin, J. Moloney, M. Buckland, A. Silvers, G. Downey, A. Molnar, M. Langley, D. McIlroy, D. Daly, P. Bennett, L. Forlano, R. Testa, W. Burnett, F. Johnson, M. Angliss, H. Fletcher; Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada (32): P. Manninen, M. Wallace, K. Lukitto, M. Tymianski, P. Porter, F. Gentili, H. El-Beheiry, M. Mosa, P. Mak, M. Balki, S. Shaikh, R. Sawyer, K. Quader, R. Chelliah, P. Berklayd, N. Merah, G. Ghazali, M. McAndrews, J. Ridgley, O. Odukoya, S. Yantha; Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina (31): J. Wilson, P. Petrozza, C. Miller, K. O'Brien, C. Tong, M. Olympio, J. Reynolds, D. Colonna, S. Glazier, S. Nobles, D. Hill, H. Hulbert, W. Jenkins; Mayo Clinic College of Medicine, Rochester, New York (28): W. Lanier, D. Piepgras, R. Wilson, F. Meyer, J. Atkinson, M. Link, M. Weglinski, K. Berge, D. McGregor, M. Trenerry, G. Smith, J. Walkes, M. Felmlee-Devine; West Fälische Wilhelms-Universitat Muenster, Muenster, Germany (27): H. Van Aken, C. Greiner, H. Freise, H. Brors, K. Hahnenkamp, N. Monteiro de Oliveira, C. Schul, D. Moskopp, J. Woelfer, C. Hoenemann, H. Gramke, H. Bone, I. Gibmeier, S. Wirtz, H. Lohmann, J. Freyhoff, B. Bauer; University of Wisconsin Clinical Science Center, Madison, Wisconsin (26): K. Hogan, R. Dempsey, D. Rusy, B. Badie, B. Iskandar, D. Resnick, P. Deshmukh, J. Fitzpatrick, F. Sasse, T. Broderick, K. Willmann, L. Connery, J. Kish, C. Weasler, N. Page, B. Hermann, J. Jones, D. Dulli, H. Stanko, M. Geraghty, R. Elbe; Montreal Neurologic Hospital, Montreal, Canada (24): F. Salevsky, R. Leblanc, N. Lapointe, H. Macgregor, D. Sinclair, D. Sirhan, M. Maleki, M. Abou-Madi, D. Chartrand, M. Angle, D. Milovan, Y. Painchaud; Johns Hopkins Medical Institutions, Baltimore, Maryland (23): M. Mirski, R. Tamargo, S. Rice, A. Olivi, D. Kim, D. Rigamonti, N. Naff, M. Hemstreet, L. Berkow, P. Chery, J. Ulatowski, L. Moore, T. Cunningham, N. McBee, T. Hartman, J. Heidler, A. Hillis, E. Tuffiash, C. Chase, A. Kane, D. Greene-Chandos, M. Torbey, W. Ziai, K. Lane, A. Bhardwaj, N. Subhas; Cleveland Clinic Foundation, Cleveland, Ohio (20): A. Schubert, M. Mayberg, M. Beven, P. Rasmussen, H. Woo, S. Bhatia, Z. Ebrahim, M. Lotto, F. Vasarhelyi, J. Munis, K. Graves, J. Woletz, G. Chelune, S. Samples, J. Evans, D. Blair, A. Abou-Chebl, F. Shutway, D. Manke, C. Beven; New York Presbyterian Hospital–Weill Medical College of Cornell University, New York, New York (15): P. Fogarty-Mack, P. Stieg, R. Eliazo, P. Li, H. Riina, C. Lien, L. Ravdin, J. Wang, Y. Kuo; Stanford University Medical Center, Palo Alto, California (15): R. Jaffe, G. Steinberg, D. Luu, S. Chang, R. Giffard, H. Lemmens, R. Morgan, A. Mathur, M. Angst, A. Meyer, H. Yi, P. Karzmark, T. Bell-Stephens, M. Marcellus; Plymouth Hospitals National Health Service Trust, Plymouth, United Kingdom (14): J. Sneyd, L. Pobereskin, S. Salsbury, P. Whitfield, R. Sawyer, A. Dashfield, R. Struthers, P. Davies, A. Rushton, V. Petty, S. Harding, E. Richardson; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (11): H. Yonas, F. Gyulai, L. Kirby, A. Kassam, N. Bircher, L. Meng, J. Krugh, G. Seever, R. Hendrickson, J. Gebel; Austin Health, Melbourne, Australia (10): D. Cowie, G. Fabinyi, S. Poustie, G. Davis, A. Drnda, D. Chandrasekara, J. Sturm, T. Phan, A. Shelton, M. Clausen, S. Micallef; Methodist University Hospital, Memphis, Tennessee (8): A. Sills, F. Steinman, P. Sutton, J. Sanders, D. Van Alstine, D. Leggett, E. Cunningham, W. Hamm, B. Frankel, J. Sorenson, L. Atkins, A. Redmond, S. Dalrymple; University of Alabama at Birmingham, Birmingham, West Midlands, United Kingdom (7): S. Black, W. Fisher, C. Hall, D. Wilhite, T. Moore II, P. Blanton, Z. Sha; University of Texas Houston Health Science Center, Houston, Texas (7): P. Szmuk, D. Kim, A. Ashtari, C. Hagberg, M. Matuszczak, A. Shahen, O. Moise, D. Novy, R. Govindaraj; University of Colorado Health Science Center, Denver, Colorado (4): L. Jameson, R. Breeze, I. Awad, R. Mattison, T. Anderson, L. Salvia, M. Mosier; University of Oklahoma Health Science Center, Oklahoma City, Oklahoma (3): C. Loftus, J. Smith, W. Lilley, B. White, M. Lenaerts.

Appendix 2. IHAST Cardiovascular Intercurrent Event Definitions

Event or Procedure	Diagnostic Criteria
Hypertension, not intended	Any instance when MAP is at or above 120 mmHg for 15 consecutive min (or longer), but this level of hypertension was not clinically desired.
Hypertension, intended	Any instance when MAP is at or above 120 mmHg for 15 consecutive min (or longer), and this level of hypertension was clinically desired. Examples: (1) induction of hypertension during temporary clipping; (2) induction of hypertension in an attempt to reverse new and worse neurologic deficits.
Hypotension, not intended	Any instance when MAP is at or below 60 mmHg for 15 consecutive min (or longer), but this level of hypotension was not clinically desired.
Hypotension, intended	Any instance when MAP is at or below 60 mmHg for 15 consecutive min (or longer), and this level of hypotension was clinically desired. Examples: induction of hypotension during the dissection and clipping phase of the aneurysm surgery, often referred to as "controlled" or "induced" or "deliberate" hypotension.
Vasopressor or inotrope administration to support systemic circulation*	Any instance when any vasopressor or inotropic agent is continuously administered for 15 consecutive min (or longer) to support the systemic circulation. Examples: (1) vasopressor or inotrope administration to treat hypotension (local definition) low systemic vascular resistance, or shock; (2) vasopressor or inotrope administration to treat low cardiac output and cardiac or pulmonary failure.
Vasopressor or inotrope administration to support cerebral circulation	Any instance when any vasopressor or inotropic agent is continuously administered for 15 consecutive min (or longer) to support the cerebral circulation. Examples: (1) vasopressor or inotrope administration to increase MAP during temporary clipping; (2) vasopressor or inotrope administration in an attempt to prevent or reverse new and worse neurologic deficits.
Vasopressor or inotrope administration for other reasons	Any instance when any vasopressor or inotropic agent is continuously administered for 15 consecutive min (or longer) for reasons that do not fall into the two other "vasopressor or inotrope" categories. Example: low-dose dopamine infusion for renal protection.
Myocardial ischemia or infarction*	Any instance when there is myocardial hypoperfusion and/or myocardial cell death mediated by inadequate coronary artery blood flow, typically associated with atherosclerotic coronary artery disease. In the setting of acute subarachnoid hemorrhage, electrocardiographic abnormalities which ordinarily indicate myocardial ischemia or infarction are not, by themselves, reliable markers. Hence, the diagnosis of myocardial ischemia and infarction in the setting of acute SAH will require, in addition to appropriate electrocardiographic changes, at least one major, or two minor, supportive clinical and laboratory signs. Major signs include (1) classic angina or the patient's anginal equivalent (with or without associated signs of nausea, diaphoresis, and anxiety); (2) a new positive pyrophosphate scan; (3) significant stenosis of an appropriate coronary artery (angiography); (4) autopsy confirmation of acute myocardial ischemia or infarction. Minor signs include (1) a new and distinct increase in serum creatine kinase-MB or troponin levels (2) associated acute hemodynamic instability; (3) associated acute pulmonary congestion (dyspnea, orthopnea, rales, and pulmonary edema); (4) a new and distinct regional wall motion abnormality.
Congestive heart failure or pulmonary edema	Any instance when clinical signs and symptoms point to abnormally high left ventricular end-diastolic pressure, resulting in translocation of fluid from the pulmonary capillaries into the pulmonary interstitial and alveolar spaces ("hydrostatic" pulmonary edema). Signs and symptoms include rales, increased jugular venous pressure, peripheral edema, dyspnea at rest or on exertion, orthopnea, S3 gallop, and radiologic evidence of pulmonary congestion (increased pulmonary vascular markings and alveolar consolidation). Although this can occur in patients with normal ventricular function, most often this is associated with compromised left ventricular function and diminished cardiac reserve. Signs of low cardiac output may include relative hypotension, pallor or cool extremities, oliguria, and low cardiac output measurements and marked wall motion or ejection abnormalities on echocardiographic examination.
Cardiogenic shock*	Any instance when there is substantively decreased cardiac output (which is not because of hypovolemia or cardiac tamponade) associated with systemic hypoperfusion (increased lactate concentration and oliguria) and hypotension (MAP at or below 60 mmHg). In the absence of inotropes, in cardiogenic shock, cardiac index is usually less than 2.2 $l \cdot m^{-2} \cdot min$ and mixed venous hemoglobin saturation is usually less than 65%.

(*continued*)

Appendix 2. Continued

Event or Procedure	Diagnostic Criteria
Supraventricular dysrhythmia (atrial fibrillation or atrial flutter and other supraventricular tachydysrhythmia)	Any instance when a supraventricular dysrhythmia is present. Atrial fibrillation: electrocardiogram demonstrates a lack of clearly defined P waves with an undulating baseline that may alternate between recognizable atrial activity or nearly a flat line. The ventricular response is irregular. Atrial flutter: electrocardiogram demonstrates "sawtooth" atrial complexes (leads II, III, and aVF) of constant morphology, polarity, and cycle length with a rate from 240–340 beats/min. The ventricular response rate to atrial flutter is frequently 2:1 or 4:1 and is regular. Other supraventricular tachydysrhythmia: any form of sustained abnormal rapid supraventricular rhythm. Examples include premature atrial complexes, premature junctional complexes, paroxysmal atrial tachycardia, multifocal atrial tachycardia, paroxysmal supraventricular tachycardia, atrioventricular nodal reentrant tachycardias. It is not necessary to specify the type of abnormality.
Sinus bradycardia	Any instance when the sinus node rate is equal to 40 beats/min or less.
Conduction blocks (atrioventricular blocks and bundle branch blocks)	Any instance when any form of atrioventricular nodal or complete bundle branch block exists. First-degree atrioventricular block: PR interval more than 0.2 s and each P wave is followed by a QRS complex. Second-degree atrioventricular block: type I (Wenckebach): progressive lengthening of the PR interval before a nonconducted P wave; type II: constant PR interval followed by a sudden failure of a P wave to be conducted to the ventricle. Third-degree atrioventricular block: dissociated P waves and QRS complexes each firing at their own pacemaker rate. The atrial impulse is never conducted to the ventricles. Bundle branch block: supraventricular rhythm with a QRS duration $\geq$ 0.120 s and no Wolf-Parkinson-White pattern. Either right or left bundle branch block qualify. Left anterior hemiblock does not qualify.
Other significant dysrhythmia	Any other clinically significant arrhythmia that is not adequately characterized by the arrhythmia criteria described earlier.
Ventricular fibrillation or ventricular tachycardia*	Any instance when either ventricular fibrillation or ventricular tachycardia is present. Ventricular fibrillation: electrocardiogram reveals irregular and rapid oscillations (250–400 beats/min) of highly variable amplitude without identifiable QRS complexes or T waves. With ventricular fibrillation, there is no coordinated ventricular contraction. As a result, immediate hemodynamic collapse always occurs. Ventricular tachycardia: any instance when there is a series of three or more consecutive wide complex (at or above 120 ms) beats at a rate at or above 100 beats/min, where the origin of electrical activation is the ventricle. The ventricular complexes can be monomorphic or polymorphic (Torsades de Pointes).
Other significant cardiovascular disorder or complication	Any other clinically significant cardiovascular disorder or complication that is not adequately characterized by the criteria earlier (*e.g.*, pericardial tamponade).
Cardioversion or defibrillation	Any instance when electrical current is directed to the heart either directly (open chest) or indirectly (closed chest) to treat a cardiac rhythm abnormality.
Cardiac pacemaker placement	Any instance when any cardiac pacemaker is placed, either internal or external, regardless of whether or not the pacemaker is, or is not, used.
Cardiopulmonary resuscitation*	Any instance when open- or closed-chest manual cardiac compression is required.
Coronary angiogram*	Any instance when any coronary angiogram is performed, regardless of specific technique.
Coronary angioplasty and stenting*	Any instance when either coronary angioplasty is performed or an intracoronary vascular stent is placed.
Cardiac surgery*	Any instance when the patient undergoes any form of cardiac surgery. Such procedures must occur in an operating room. This does not include angiographic procedures.
Vascular surgery	Any instance when the patient undergoes any form of vascular surgery. Such procedures must occur in an operating room.
Electrocardiogram	Any instance when an electrocardiogram is performed, regardless of the reason for the examination.
Echocardiogram	Any instance when an echocardiogram is performed (transthoracic or transesophageal), regardless of the reason for the examination.
Other cardiovascular procedure, intervention, or surgery	Any instance when the patient undergoes any other clinically significant cardiovascular procedure, test, or intervention that does not fall into the above procedure categories, (*e.g.*, intraaortic balloon pump, pulmonary angiogram).

* "Indicator" event; see Materials and Methods for details.

MAP = mean arterial pressure; MB = muscle brain type; SAH = subarachnoid hemorrhage.