Safety of deliberate intraoperative and postoperative hypothermia for patients undergoing coronary artery surgery: A randomized trial

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Background: Hypothermia in the perioperative period is associated with adverse effects, particularly bleeding. Before termination of cardiopulmonary bypass, rewarming times and perfusion temperatures are often increased to avoid post-cardiopulmonary bypass hypothermia and the presumed complications. This practice may, however, also have adverse effects, particularly cerebral hyperthermia. We present safety outcomes from a trial in which patients undergoing coronary artery surgery were randomly assigned to normothermia or hypothermia for the entire surgical procedure.

Methods: Consenting patients over the age of 60 years presenting for a first, elective coronary artery surgery with cardiopulmonary bypass were randomly assigned to having their nasopharyngeal temperature maintained at either 37°C (group N; 73 patients) or 34°C (group H; 71 patients) throughout the intraoperative period, with no rewarming before arrival in the intensive care unit. All received tranexamic acid.

Results: There was no clinically important difference in intraoperative blood product or inotrope use. Temperatures on arrival in the intensive care unit were 36.7°C $\pm$ 0.38°C and 34.3°C $\pm$ 0.38°C in groups N and H, respectively. Blood loss during the first 12 postoperative hours was 596 $\pm$ 356 mL in group N and 666 $\pm$ 405 mL in group H (mean difference $\pm$ 95% confidence interval, 70 $\pm$ 126 mL; $P = .28$). There was no significant difference in blood product utilization, intubation time, time in the hospital, myocardial infarction, or mortality. The mean time in the intensive care unit was 8.4 hours less in the hypothermic group ($P = .02$).

Conclusions: Our data support the safety of perioperative mild hypothermia in patients undergoing elective nonreoperative coronary artery surgery with cardiopulmonary bypass. These findings suggest that complete rewarming after hypothermic cardiopulmonary bypass is not necessary in all cases.

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dverse effects of hypothermia are an important concern in surgical patients, with an expanding literature documenting complications, particularly bleeding, when body temperature is not maintained at $>36^{\circ}\text{C}$ in the perioperative period.¹ Hypothermia has, however, been shown to be neuroprotective in laboratory studies, as well as in 2 recent randomized clinical trials of survivors of out-of-hospital cardiac arrest.^{2,3} These findings encourage clinical trials of mild hypother-

mia in other populations of patients at risk of cerebral injury.⁴ Although there are numerous trials of cardiopulmonary bypass (CPB) at warm and cold temperatures,^{5,6} in all studies patients are rewarmed to at least 36°C before separation from CPB. The reluctance to separate from CPB at hypothermic temperatures is likely due to the belief that patient safety would be compromised. A recent large retrospective database study⁷ concluded that patients who arrive in the intensive care unit (ICU) after coronary artery surgery with a temperature <36°C are at significantly increased risk of death, excessive bleeding, and other complications compared with normothermic patients. Complete rewarming of patients who have been cooled to ≤34°C requires either rewarming of the blood in the pump oxygenator to temperatures >38°C, which may be detrimental to the brain,⁸ or rewarming slowly and prolonging CPB time, which is also associated with adverse effects. In weighing the risks and benefits of a temperature management strategy for CPB, it is essential to have an unbiased estimate of the consequences of not completely rewarming the patient. We have recently completed a randomized clinical trial of the neuroprotective effect of mild hypothermia for patients undergoing coronary artery bypass grafting (CABG).⁹ Our results suggest that mild hypothermia decreases the incidence and severity of cognitive deficits. This is the only trial in which hypothermia was extended into the postoperative period, and there was no clinically important difference in bleeding or other safety outcomes between the hypothermic and control groups. However, both groups were hypothermic on arrival in the ICU: 35.3°C ± 0.6°C and 33.6°C ± 0.5°C (mean ± SD). In the present trial, we have been able to maintain constant temperature throughout the operative period until arrival in ICU: normothermia in the control group and 34°C in the hypothermic group. This provided a unique opportunity to explore the safety of mild hypothermia versus true normothermia in comparable groups of cardiac surgical patients. We present here an analysis of our safety data and a comparison of our results with the published literature. We believe that these data can help those caring for cardiac surgical patients to make a more informed decision about the optimal temperature management for their patients.

Materials and Methods

Patients

Between October 2000 and October 2002, patients older than 60 years who were scheduled to undergo nonemergency coronary artery surgery at the University of Ottawa Heart Institute were asked for informed consent for enrollment in this trial, which was approved by our institutional review board. Because the primary outcome of the trial was postoperative cognitive function, we excluded patients with neurological deficits. Patients with serum creatinine more than twice normal and those with a history of cardiac surgery were also excluded. At the time of the safety data analysis presented here, 144 patients had been studied.

Protocol and Randomization

Anesthesia was induced with midazolam and sufentanil and maintained with isoflurane, as well as with sufentanil and midazolam or propofol infusions. All patients were monitored with a radial arterial line and pulmonary artery catheter. After the induction of anesthesia, a temperature probe was placed in the nasopharynx, and this temperature was monitored and controlled throughout the intraoperative period. Bladder temperature was used as an indicator of visceral temperature. Tranexamic acid (1-g bolus after induction and a 2.0 mg/kg/h intraoperative infusion) was administered to all patients.

Eligible and consenting patients were equally assigned to hypothermia or normothermia by using a computer-generated randomization list. The randomization was stratified according to age ≤75 years, and blocks of 8 were used. Treatment assignment was concealed in opaque sealed envelopes that were assigned sequentially as patients were enrolled, according to age block. The study coordinator opened the envelope 30 minutes before operation. Patients were unaware of the treatment assignment, which was not concealed from the clinical staff. Patients in the normothermic group were warmed with a forced-air heating blanket for 15 to 30 minutes before entering the operating room. On arrival in the operating room, high-efficiency thermal pads were applied to the patient's back and posterior aspect of the upper leg. The pads were connected to a water-circulating thermal control system (Arctic Sun; Medivance Corporation, Louisville, Colo), and cooling to 34°C or warming to 37°C was begun. Patients were kept as close as possible to nasopharyngeal temperatures of 37°C or 34°C throughout the intraoperative period. CPB was performed via an ascending aortic cannula and a 2-stage right atrial cannula with membrane oxygenators and 43-μm arterial line filters (Cobe Cardiovascular, Arvada, Colo) with a nonpulsatile flow at 2.5 to 2.8 L/min/m². Mean arterial pressure was maintained between 50 and 80 mm Hg by using phenylephrine or isoflurane. Blood gases were not temperature corrected. The heater/cooler was needed only to make small corrections in temperature during CPB; the temperature of blood leaving the oxygenator was monitored and recorded and was not allowed to exceed 37.5°C or 34.5°C in the normothermic and hypothermic groups, respectively. After application of the aortic crossclamp, cardiac arrest was induced and maintained with antegrade cold crystalloid cardioplegia. Proximal anastomoses were fashioned by using a side-biting clamp on the aorta. Nasopharyngeal temperatures were kept constant at 34°C or 37°C until arrival in the ICU. In the ICU, forced-air warming blankets were applied. The transfusion protocol conformed with the guidelines at our institution, which are to ensure that hematocrit is >20% before separating the patient from CPB. After CPB and in the ICU, hematocrit is maintained >24%. Guidelines for reopening were blood loss >500 mL in 1 hour or 1000 mL in 4 consecutive hours. Inotropes were used if the cardiac index was less than 2.2 L/min/m² in the presence of adequate preload. Patients were extubated if they were responsive and hemodynamically stable, temperature was >36°C, chest tube drainage was <100 mL/h, P_{AO₂} was >80 mm Hg on F_{IO₂} ≤50%, pH was >7.3, P_{CO₂} was <50 on continuous positive airway pressure of 8 cm H₂O and pressure support of 10 cm H₂O, respiratory rate was <25 breaths/min, and tidal volume was >5 mL/kg. To be discharged from the ICU, patients had to be off all vasoactive drug infusions,

TABLE 1. Preoperative characteristics of the patients*

Characteristic	Normothermic (n = 73)	Hypothermic (n = 71)
Age (y)	70 ± 7	68 ± 6
Male sex	61 (84)	64 (90)
Left ventricular ejection fraction >35%	61 (84)	64 (90)
CCS		
1 and 2	23 (32)	21 (30)
3	31 (43)	36 (51)
4	19 (26)	14 (20)
NHYA		
I	65 (89)	62 (87)
II	5 (7)	6 (8)
III	3 (4)	3 (4)
Diabetes mellitus		
Diet or oral medication	25 (35)	17 (23)
Insulin	3 (4)	5 (7)

CCS, Canadian Cardiovascular Society angina classification; NYHA, New York Heart Association functional classification.

*Data are mean ± SD or n (%).

have SpO₂ >90% with ≤50% oxygen by mask, have a respiratory rate of 10 to 25 breaths/min, have chest tube drainage <50 mL/h, and have urine output >0.5 mL/kg/h. Criteria for discharge from the hospital included the ability to tolerate a light diet and to ambulate 120 m and 9 stairs with no more than a 30-beat/min increase in HR, and SpO₂ >90%.

Outcomes

During surgery, we recorded nasopharyngeal, bladder, and oxygenator outlet temperatures, the use of blood products and inotropic drugs, time on CPB, and aortic crossclamp time. The quantity of phenylephrine and Ringer's lactate administered during CPB was measured. Bleeding from the chest and mediastinal tubes was measured hourly during the first 12 postoperative hours. The use of blood products and inotropes after surgery was also recorded. Time until extubation, days in the ICU, and days in the hospital were noted. Electrocardiograms taken 2 hours, 1 day, and 2 to 5 days after surgery were assessed. Myocardial infarction was defined as the appearance of new Q waves >0.04 seconds in duration in at least 2 contiguous leads. Creatine kinase (CK) was measured on the morning after surgery. Troponin T was determined if the total CK was greater than 900 U/L. Chest and leg wound infections were documented by the infection control service by using established definitions.¹⁰

Statistical Analysis

The primary analysis was by treatment group (normothermia or hypothermia), with no exclusions. All patients received the assigned treatment. These data are based on a midpoint safety analysis of a trial of the neuroprotective effect of mild hypothermia. The sample size for the full trial is 300 analyzable cases. A sample size of 150 provides 80% power (with $\alpha = .05$) to detect a difference in 12-hour postoperative chest tube losses of 250 mL on the basis of the SD from our previous study⁹ of 542 mL. Data are presented as mean ± SD or median ± interquartile range. Continuous variables were compared by using unpaired *t* tests if

normally distributed or the Mann-Whitney test otherwise. Categorical data were compared by using a χ^2 test or the Fisher exact test when an expected cell value was <5.

Results

The preoperative characteristics (Table 1) of the 73 patients randomly assigned to normothermia and the 71 assigned to hypothermia were similar. At the time of aortic cannulation, the normothermic group was 0.7°C below the target temperature, and the hypothermic group was 0.5°C above the target (Table 2). The target temperatures were achieved soon after the initiation of CPB. At the end of CPB, both groups were at the target temperatures, and there was no gradient between nasopharyngeal and bladder temperature. On arrival in the ICU, the temperature was the same at all sites and was within 0.3°C of the target in both groups. There was no clinically important difference in intraoperative use of allogeneic packed red blood cells or inotrope infusions. No patient required the use of the intra-aortic balloon pump. More phenylephrine was required to maintain mean arterial pressure in the normothermic group. The hypothermic group received more crystalloid during CPB. Postoperative (Table 3) safety outcomes were similar between groups. The mean difference in 12-hour postoperative blood loss between groups was 70 mL, with a 95% confidence interval including the hypothermic group losing 196 mL more to 56 mL less blood than the normothermic group. Blood product use was nearly identical. Two patients from each group returned to the operating room for excessive bleeding. Within 4 hours of arrival in the ICU, 90% of patients in the hypothermic group had rewarmed to ≥36°C. During the first 12 hours in the ICU, there was no significant difference between groups in the frequency of use of inotropes or nitroprusside. There were 4 patients with Q-wave myocardial infarctions (2 in each group). Creatinine kinase levels were 673 ± 564 IU and 524 ± 276 IU in the normothermic and hypothermic groups, respectively ($P = .42$; Mann-Whitney test). There was a bimodal distribution of CK; 14 patients in the normothermic group and 4 in the hypothermic group had levels >900 U/L ($P = .015$; χ^2 test). Troponin T was determined in these patients (mean ± SD: normothermic, 0.74 ± 0.46 ng/mL; hypothermic, 0.67 ± 0.13 ng/mL; $P = .915$). The length of ICU stay was 8.4 hours less in the hypothermic group. Wound infections developed in 3 patients within 30 days of operation: 2 in the normothermic group and 1 in the hypothermic group. There were 2 deaths in the hospital, both in the hypothermic group and both on the day of operation. The probable cause of death in 1 patient was cardiogenic shock due to a perioperative myocardial infarction. The other patient became hypotensive and was reopened but could not be resuscitated. Both patients had temperatures >36°C before becoming hemodynamically unstable.

TABLE 2. Operative characteristics*

Characteristic	Normothermic (n = 73)	Hypothermic (n = 71)	P value
Cardiopulmonary bypass time (min)	77 ± 19	73 ± 19	.30
Aortic crossclamp time (min)	45 ± 14	44 ± 15	.70
Coronary artery bypass grafts	3 ± 0.7	3 ± 0.6	.18
Glucose† (mmol/L)	7 ± 1.5	7 ± 1.2	.22
Hematocrit†	25 ± 4.1	25 ± 3.6	.92
Patients receiving intraoperative allogeneic red blood cells	7 (9.6%)	4 (5.6%)	.37
Phenylephrine during CPB (mg)‡	2.0 (2.6)	0.5 (1.1)	<.001
Ringer's lactate on CPB (L)	2.67 ± 0.74	2.96 ± 0.68	.015
Nasopharyngeal temperature at aortic cannulation (°C)	36.3 ± 0.43	34.5 ± 0.60	<.0001
Nasopharyngeal temperature at start of cardiopulmonary bypass (°C)	36.3 ± 0.45	34.3 ± 0.60	<.0001
Bladder temperature at start of cardiopulmonary bypass (°C)	36.4 ± 0.40	35.0 ± 0.66	<.0001
Nasopharyngeal temperature at end of cardiopulmonary bypass (°C)	37.0 ± 0.17	34.1 ± 0.13	<.0001
Bladder temperature at end of cardiopulmonary bypass (°C)	37.0 ± 0.15	34.1 ± 0.19	<.0001
Inotrope infusions	6 (8%)	3 (4%)	.49
Temperature on arrival in ICU (°C)§	36.7 ± 0.38	34.3 ± 0.38	<.0001

CPB, Cardiopulmonary bypass; ICU, intensive care unit.

*Data are mean ± SD or n (%) unless otherwise noted.

†Measured after protamine administration; 1 mmol/L = 18.02 mg/dL.

‡Median (interquartile range).

§Temperatures were equal at all sites by the time of arrival in the ICU.

Discussion

In patients undergoing CABG surgery who were randomly assigned to a constant intraoperative temperature of 34°C or 37°C, we found no clinically important effect of temperature management on perioperative complications. These results support the finding of our previous series of 223 patients, in which a 2°C to 3°C temperature difference had no effect on morbidity or mortality.⁹ In the previous study, on arrival in the ICU both groups were mildly hypothermic, with a mean temperature of 35.3°C in the control group and 33.6°C in the hypothermic group. In this study, true normothermia was maintained in the control group and proved to confer no advantage to the patients. The fact that intraoperative hypothermia extending into the postoperative period did not have a significant effect on blood loss or blood product use indicates that temperature in the range measured, in this patient population, does not have an important effect on postoperative bleeding. All patients received tran-

TABLE 3. Safety outcomes*

Outcome	Normothermic (n = 73)	Hypothermic (n = 71)	P value
Hours ventilated in ICU	10.9 ± 8.4	11.0 ± 7.8	.93
Days in ICU	1.56 ± 1.1	1.21 ± 0.7	.02
Median	1.07	0.98	.014
Days in hospital	6.5 ± 3.3	6.3 ± 2.2	.65
Median	5.0	5.0	
12-h blood loss in ICU (mL)	596 ± 356	666 ± 405	.28
Blood utilization in ICU			
Allogeneic red blood cells (U)	0.7 ± 1.4	0.7 ± 1.2	.76
Number of patients (%)	23 (32)	24 (34)	.77
Fresh frozen plasma (U)	0.2 ± 0.9	0.4 ± 1.2	.38
Number of patients (%)	3 (4)	5 (7)	.44
Platelets (U)	0.1 ± 0.9	0.1 ± 0.7	.87
Number of patients (%)	1 (1.4)	1 (1.5)	.98
Any blood product			
Number of patients (%)	25 (34)	29 (41)	.41
Reopened for bleeding (%)	2 (2.7)	2 (2.9)	1.0
Inotrope use (%)	16 (22)	11 (15)	.32
Nitroprusside (%)	29 (40)	31 (44)	.63
Mortality (%)	0 (0)	2 (3)	.23

ICU, Intensive care unit.

*Data are mean ± SD unless otherwise noted.

examic acid, and this may account for the fact that blood loss in both groups was approximately 200 mL less than in our previous study. There was no increase in time to extubation associated with hypothermia, although these results may not apply to institutions desiring earlier extubations. The fact that 90% of the hypothermic patients had temperatures ≥36°C within 4 hours of arrival in the ICU suggests that rewarming need not delay extubation beyond 4 hours in most patients. Time spent in the ICU was 9.6 hours, or 24%, shorter in the hypothermic group. We have no explanation for this difference. Hospital length of stay was the same for both groups. This study was not powered to demonstrate a difference in wound infection rate or myocardial infarction; to show a difference between 5% in 1 group compared with 7.5% in the other, with an α of .05 and a power of 80%, would require 1549 patients per group. It is difficult to interpret the importance of enzyme release after cardiac surgery. In a recent study, Januzzi and associates¹¹ found that patients without cardiac complications after cardiac surgery had mean ± SD troponin T levels of 0.89 ± 0.75 ng/mL 18 to 24 hours after surgery, compared with 8.43 ± 9.10 ng/mL in patients with complications. Mean troponin T levels were <0.89 ng/mL in both groups in this study; however, because myocardial-specific enzyme results were available in only a few patients, it is impossible to interpret the results with confidence. The incidence of Q-wave myocardial infarction was not different between groups.

The association between hypothermia and adverse outcome is most evident in trauma, where injured patients presenting to the emergency room with temperatures of

$\leq 32^{\circ}\text{C}$ have a mortality of 100%.¹² Despite laboratory evidence of a possible benefit of hypothermia in shock,¹³ a randomized study of delayed rewarming in trauma patients demonstrated increased fluid requirements in the hypothermic group and an increased early mortality.¹⁴ Sessler¹ has comprehensively reviewed the adverse effects of mild perioperative hypothermia. These include increased incidence of wound infection, increased bleeding, cardiac events, delayed recovery from anesthesia, postoperative shivering, and thermal discomfort. Schmied and colleagues¹⁵ randomized patients undergoing hip surgery to active warming or conventional treatment. The warmed patients left the operating room at a temperature of 36.6°C , compared with 35.0°C in the control patients. Perioperative blood loss was 25% less in the normothermic group. This is supported by laboratory evidence of prolongation of coagulation factor kinetics^{16,17} and platelet dysfunction¹⁸ with hypothermia. Kurz and colleagues¹⁹ and Melling and associates²⁰ have published randomized controlled trials demonstrating a reduced incidence of wound infection with warming in patients undergoing clean-contaminated or clean operation, respectively. The increased susceptibility to wound infection may be due to decreased tissue oxygen tension secondary to cutaneous vasoconstriction in response to hypothermia.²¹ Frank and associates²² provide evidence of an increased incidence of cardiac events after major operation in patients with proven ischemic heart disease or at high risk of ischemic heart disease in whom mild hypothermia was allowed to develop. Unlike the study of Frank and associates, patients in this study were revascularized.

There are no studies, other than the present research, that randomize cardiac surgical patients to perioperative hypothermia compared with normothermia. There are numerous studies of the effects of differing temperatures confined to the period during which the patient is on CPB. Of 6 studies that reported perioperative blood loss, 5 studies²³⁻²⁷ found no difference, and 1 study²⁸ showed increased loss in the hypothermic group. The Cochrane Library⁵ recently published a review of 17 randomized controlled trials comparing hypothermia and normothermia during CPB. They found a trend for a reduced incidence of stroke in the hypothermic group and a trend for increased non-stroke-related perioperative deaths in the hypothermic group. When all bad outcomes were considered (cardiac and neurological), there was no difference related to temperature. The only publication reporting the effect on outcome of postoperative hypothermia in cardiac surgical patients is a large retrospective database analysis including 5701 patients undergoing isolated CABG.⁷ Patients arriving in the ICU with temperatures $< 36^{\circ}\text{C}$ were considered hypothermic. After adjusting for severity of illness and intraoperative risk factors, it was found that the normothermic group had a significantly lower risk for death (odds ratio, 0.59; 95%

confidence interval, 0.39-0.91) and transfusion (odds ratio, 0.61; 95% confidence interval, 0.54-0.69). Duration of mechanical ventilation and ICU and hospital length of stay were all increased in the hypothermic patients. The results of this retrospective study are in contrast with the results of the present study and our previous study.⁹ Only a randomized trial can generate comparable groups in which both known and unknown prognostic factors are balanced. In our previous study, we were unable to prevent cooling of patients after separation from CPB, and patients arrived in the ICU with temperatures ranging from 32.6°C to 35.3°C in the hypothermic group and 33.6°C to 36.5°C in the control group. Although mean blood loss in the 2 groups was not significantly different (control, 812 ± 493 mL; hypothermic, 858 ± 592 mL; mean $\pm$ SD; $P = .53$), this distribution of temperatures allowed us to perform multiple-regression analysis to identify factors that might explain the dispersion of temperatures among patients randomly assigned to the same group. We found that the patients from our previous study, who arrived in the ICU with temperatures most below the rewarming target, were more likely to have had a prolonged CPB time and more blood transfusions (fluid warmers were not used in Insler and associates'⁷ study or our previous study). It is possible that patients with lower temperatures on arrival in the ICU in Insler and associates' study were those in whom surgical difficulties were encountered that prolonged operation or resulted in increased bleeding. These difficulties may have been the true cause of the poor outcomes. Thus, postoperative hypothermia may have been a correlate of poor outcome, but not the cause.

Rapid rewarming before terminating hypothermic CPB requires heating the blood in the oxygenator to $\geq 39^{\circ}\text{C}$.²⁹ The brain rapidly warms to the temperature of the blood, and the resulting cerebral hyperthermia is generally believed to be injurious.⁸ Avoiding heating the blood to temperatures $> 37^{\circ}\text{C}$ to 38°C would necessitate prolonged rewarming times if body temperature is to be restored to 37°C . If mild perioperative hypothermia is safe, then patients need not be completely rewarmed before separating from CPB, and the deleterious effects of cerebral hyperthermia, as well as prolonged CPB, can be avoided. This strategy would become even more compelling if our recent findings of a neuroprotective effect of extended mild hypothermia for patients undergoing CABG were confirmed.⁹

The present research is the only randomized trial comparing hypothermia with normothermia throughout the entire intraoperative period in patients undergoing coronary artery surgery. Our data support the safety of perioperative mild hypothermia in patients undergoing elective nonreoperative coronary artery surgery with CPB.

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