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Deliberate Mild Intraoperative Hypothermia for Craniotomy

Kristy Z. Baker, M.D., William L. Young, M.D.,† J. Gilbert Stone, M.D.,‡ Abraham Kader, M.D.,§ Christopher J. Baker, M.D.,§ Robert A. Solomon, M.D.‖*

Background: **Despite enthusiasm for the use of mild hypothermia during neurosurgical procedures, this therapy has not been evaluated systematically. This study examined the feasibility and safety of deliberate mild hypothermia and rewarming.**

Methods: **Thirty patients scheduled for craniotomy were assigned to either a normothermic or mildly hypothermic group. Tympanic membrane temperature was monitored at anesthetic induction, throughout the isoflurane–fentanyl–N_2O–O_2 anesthetic, and for 18 h postoperatively. Normothermic patients were warmed to 36.5–37.0°C after an initial temperature decrease, and hypothermic patients were cooled to 35°C. In the hypothermic group temperatures were allowed to drift to 34.5°C before rewarming was initiated. Water blankets and convective heating devices were used to cool and rewarm.**

Results: **The minimum temperature achieved by the hypothermic group was 34.3 ± 0.4°C. Cooling occurred at a rate of 1.0 ± 0.4°C/h. Rewarming took place at a rate of 0.7 ± 0.6°C/h (range 0.1–1.8) in the hypothermic group. Hypothermia did not delay emergence from anesthesia (20 ± 15 min) compared with normothermia (15 ± 15 min, $P = .45$). Mean temperature upon intensive care unit admission was 35.8 ± 1.0°C for the hypothermic group and 37.1 ± 0.5°C for the normothermic group ($P < 0.0001$). The hypothermic patients had more postoperative shivering. From 8 to 18 h postoperatively the temperatures of the two groups were similar except for a slightly greater temperature in the hypothermic patients at 12 h (37.6 ± 0.5 *vs.* 37.3 ± 0.4°C, $P = .029$).**

Conclusions: **Although deliberate mild hypothermia is easily achieved intraoperatively, complete rewarming may be difficult to attain during craniotomy with current methods. In addition to the need for determining whether deliberate mild hypothermia confers cerebral protection in humans, the potential risks of the therapy need to be further characterized. (Key words: Anesthesia: neurosurgical. Temperature: hypothermia.)**

THERE is renewed enthusiasm for the use of deliberate hypothermia during neurologic surgery. Deep hypothermia with cardiopulmonary bypass and circulatory arrest is used selectively at several institutions in the surgical management of complex intracranial aneurysms.[1–3] Moderate hypothermia was first demonstrated to be associated with cerebral protection nearly 40 yr ago, but its clinical use declined because of an unacceptable complication rate.[4,5] Investigations in animals suggest that even mild hypothermia (core temperature decreases of as little as 1.5–3.0°C) has a significant protective effect against cerebral ischemic damage.[6–8]

Inadvertent mild hypothermia is often attained during general anesthesia, and some neurosurgical centers are routinely using deliberate mild hypothermia during surgery involving cerebral vascular occlusion when the risk of ischemic damage is high.[9] However, no systematic evaluation of deliberate mild hypothermia exists in humans. This study was designed to examine the safety of deliberate mild hypothermia and to evaluate techniques for cooling and rewarming during craniotomy.

Materials and Methods

With institutional approval, patients scheduled for elective craniotomy for supratentorial tumor resection or aneurysm repair were assigned to one of two groups

* Neuroanesthesia Fellow, Department of Anesthesiology.

† Associate Professor of Anesthesiology (in Neurological Surgery), Departments of Anesthesiology and Neurological Surgery.

‡ Associate Professor of Anesthesiology, Department of Anesthesiology.

§ Postdoctoral Residency Fellow in Neurological Surgery, Department of Neurological Surgery.

‖ Associate Professor of Clinical Neurological Surgery, Department of Neurological Surgery.

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Address correspondence to Dr. Young: Neuroanesthesia, DAP Room 901, College of Physicians and Surgeons of Columbia University, 161 Fort Washington Avenue, New York, New York 10032.

whose intraoperative temperature was either kept normothermic or made mildly hypothermic. The surgical team was not consistently blinded to temperature treatment. Patients with a history or symptoms of coronary artery or cerebrovascular atherosclerotic disease were excluded, as were patients with hypothyroidism and sepsis. Only patients operated on while supine were included. Preoperative 12-lead electrocardiograms (ECGs) were obtained, and preoperative temperatures were determined with a tympanic membrane probe (First Temp Genius, Intelligent Medical Systems, Carlsbad, CA).

Before induction of general anesthesia, routine monitors were placed, including a radial arterial catheter, noninvasive blood pressure cuff, and five-lead continuous ECG. In addition, both a tympanic membrane temperature probe (contralateral to the operative site) and an esophageal probe (Mon-a-therm, Mallinckrodt Anesthesia Products, St. Louis, MO) were inserted. Premedication with midazolam (0.03–0.05 mg/kg) and fentanyl (1.5–5 μg/kg) was followed by the induction of general anesthesia with sodium thiopental (3–7 mg/kg). Vecuronium (0.1–0.2 mg/kg) was administered to facilitate tracheal intubation. Anesthesia was maintained with isoflurane, fentanyl, N_2O, and O_2. Esmolol, labetalol, hydralazine, and phenylephrine were administered at the discretion of the anesthesiologist to maintain the blood pressure and heart rate within 10–15% of baseline.

Operating room temperature was maintained at 18–20°C. A water blanket (Hyper-hypothermia Blanket II, Cincinnati Sub-Zero, Cincinnati, OH) was placed under each patient. A convective device blanket (Warm Touch, Mallinckrodt Medical or Bair Hugger, Augustine Medical, Eden Prairie, MN) was applied directly to the ventral body surface and covered with a single cotton blanket. The temperature of normothermic patients was maintained at 36.5–37.0°C during the craniotomy. Hypothermic patients were cooled with the water blanket set at 25°C and the convective device circulating room temperature air. Active cooling was stopped at a body temperature of 35°C, and the body temperature was allowed to drift downward. Warming therapy was then titrated to maintain the core body temperature at 34.5°C. At dural closure, aggressive rewarming was initiated with the water blanket set at 40°C and the convective warmer at its highest setting (43°C).

Temperatures were recorded at the following times: anesthesia induction, skin incision, dural opening, dural closure, discontinuation of the volatile anesthetic, completion of the head wrap, tracheal extubation, arrival in the intensive care unit, and thereafter, every 2 h for 12 h, and 18 h postoperatively. Temperature in the intensive care unit was obtained from a tympanic membrane probe. Patients did not receive rewarming therapy in the intensive care unit beyond cotton blankets.

In three patients, intraoperative tympanic membrane temperature was not available because of probe malfunction and esophageal temperature was substituted. Postoperative tympanic membrane temperature was not available for one patient, and in this patient pulmonary artery catheter blood temperature was used.

Upon arrival in the intensive care unit, the degree of shivering was assessed by an nonblinded observer (KZB) and scored as none, mild, moderate or profound. ECGs were repeated on the first postoperative day; patients with ECG changes or increased blood concentrations of creatinine phosphokinase (CPK) had CPK fractionation performed.

Data were analyzed by repeated measures analysis of variance with normothermia and hypothermia as the main intergroup factor or linear regression. Comparisons by *post hoc* analysis of variance was done with Fisher's protected least-significant-differences test. Demographic and outcome variables were analyzed by Fisher's exact test. For repeated-measures analysis of variance, missing values were replaced with the mean value of the main grouping factor. Significance was assumed at $P < 0.05$.

Results

Thirty patients were studied. Fifteen patients refused randomization and were assigned at the surgeon's request to hypothermia (five aneurysm patients) or normothermia (seven patients with mass lesions, one intractable seizure patient, and two aneurysm patients). The groups did not differ significantly with respect to age, weight, body surface area, gender, ASA physical status, length of surgical procedure, or incidence of diabetes, hypertension, and hypercholesterolemia (tables 1 and 2). There was no difference between the groups in the time elapsed from anesthesia induction to the various times of temperature data collection.

The minimum temperatures reached by the two groups were significantly different (34.3 ± 0.4 *vs.* 35.7 ± 0.5°C; $P < 0.0001$), as were the temperatures at skin incision, dural opening, dural closure, discontin-

Table 1. Preoperative Demographic Data

	Normothermia	Hypothermia
n	17	13
Gender (M/F)	8/9	5/8
ASA class (II/III)	11/6	4/9
Aneurysm	4/17	10/13*
Mass lesion	11/17	3/13*
Other lesion	2/17	0/13
Essential hypertension	4/17	2/13
Tobacco use	5/16	6/12
Cholesterol >300 mg/dl	2/16	1/12
Diabetes mellitus	0/17	0/13
Digoxin use	0/17	0/13
Chronic pulmonary disease	0/17	0/13
Age (yr)	52 ± 14	46 ± 11
Weight (kg)	75 ± 14	73 ± 16
Height (cm)	167 ± 13	169 ± 6
Body surface area (m^2)	1.83 ± 0.21	1.82 ± 0.19

Parametric data reported as mean ± SD.

* Significantly different from normothermia, $P < 0.05$.

uation of the volatile anesthetic, completion of the head wrap, extubation, arrival in the intensive care unit, and 12 h postoperatively (fig. 1). Upon arrival in the intensive care unit the hypothermic patients had a temperature of 35.8 ± 1.0°C and the normothermic patients had a temperature of 37.1 ± 0.5°C ($P < 0.0001$). From 2 to 6 h postoperatively there was no significant difference in temperature between the hypothermic and normothermic groups. From 8 to 18 h postoperatively the temperatures in the two groups were similar except for a slightly greater temperature in the hypothermic group at 12 h postoperatively (37.6 ± 0.5 *vs.* 37.3 ± 0.4°C, $P = .029$) (fig. 1).

Table 2. Experimental Observations

	Normothermia	Hypothermia
Length of procedure (min)	270 ± 142	214 ± 83
Cooling rate (°C/h)	—	1.0 ± 0.4
Rewarming rate (°C/h)	—	0.7 ± 0.6
Time to extubation (min)	15 ± 15	20 ± 15
Intensive care unit arrival temperature (°C)	37.1 ± 0.5	35.8 ± 1.0*
12-Lead electrocardiographic change	1/14	2/11
Shivering	0/16	7/12*
Postoperative temperature > 38°C	6/16	8/13

Parametric data reported as mean ± SD.

Shivering was graded as mild (3/12 patients) or moderate (4/12 patients).

* Significant at $P < 0.05$.

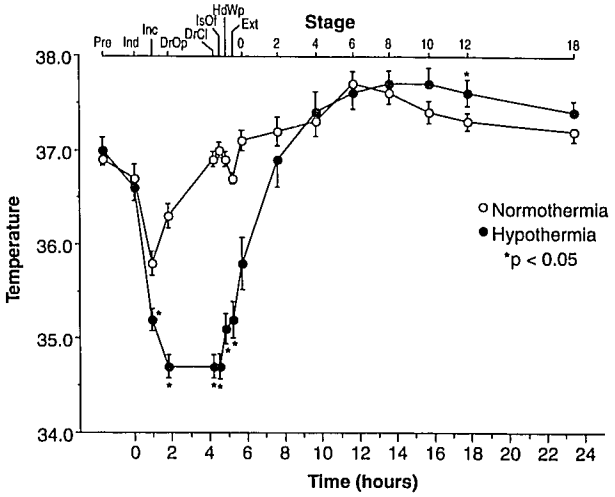

Fig. 1. Temperature *versus* operative stage for normothermic and hypothermic groups. Temperatures (mean ± SEM) were recorded at the following times: induction (Ind), incision (Inc), dural opening (Dr Op), dural closure (Dr Cl), discontinuation of the volatile anesthetic (Is Of), completion of the head wrap (Hd Wp), extubation (Ext), arrival in the intensive care unit (O), and thereafter every 2–6 h (*i.e.*, at 2, 4, 6, 8, 10, 12, and 18 h). *Significantly different from normothermia, $P < 0.05$.

The hypothermic patients cooled at a rate of 1.0 ± 0.4°C/h (range, 0.4–1.5°C/h). Rewarming from the minimum temperature to arrival in the intensive care unit was achieved at a rate of 0.7 ± 0.6°C/h (range, 0.1–1.8°C/h). Five of 13 hypothermic patients were completely rewarmed intraoperatively and arrived in the intensive care unit with a temperature greater than 36.5°C. Rewarming rates were inversely correlated with body surface area ($r = 0.66$) (fig. 2).

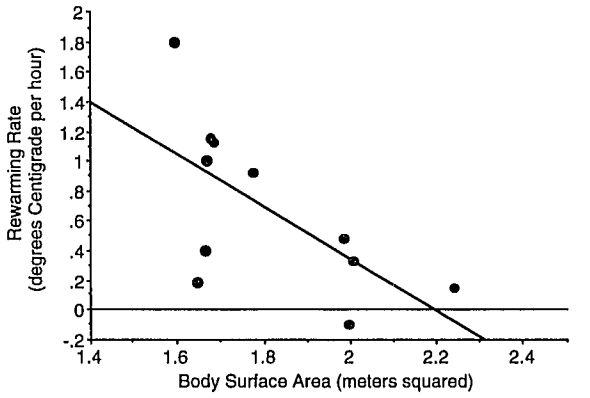

Fig. 2. Rewarming rate (degrees centigrade per hour) *versus* body surface area (meters squared) for hypothermic patients.

Deliberate mild hypothermia with rewarming did not cause significant delays in emergence from anesthesia. The time elapsed from completion of the head wrap to tracheal extubation was 20 ± 15 min for the hypothermic patients, and 15 ± 15 min for the normothermic patients ($P = 0.45$).

None (0 of 16 reported) of the normothermic patients shivered postoperatively, but 7 of 12 hypothermic patients did shiver ($P = 0.002$). Three had mild shivering and four had moderate shivering.

There were no instances of perioperative myocardial infarction. Three patients had postoperative ECG changes, but these were not associated with positive CPK cardiac isoenzymes. One hypothermic patient had nonspecific T-wave changes on the 12-lead ECG on postoperative day 1. One hypothermic and one normothermic patient each had laterally inverted T waves by ECG on the first postoperative day. One normothermic patient had rate-related T-wave inversions intraoperatively; his postoperative ECG was without change, and results of his CPK fractionation also were negative. In addition, one hypothermic patient receiving postoperative hypertensive hypervolemic therapy for cerebral vasospasm developed atrial fibrillation and ventricular bigeminy during high dose dopamine infusion. The arrhythmias began 5 h after the patient had returned to normal body temperature and ceased when phenylephrine was substituted for dopamine. The patient did not show evidence of myocardial infarction by serial ECGs and CPKs.

Discussion

The results of this study suggest that patients undergoing craniotomy can be deliberately cooled to a body temperature approaching levels shown to offer cerebral protection in animal models. Rewarming occurs at variable rates with conventionally available devices, and an intraoperative return to normothermia is not always easy to achieve. Deliberate hypothermia and incomplete rewarming caused a significantly greater degree of postoperative shivering than did maintenance of normothermia.

The rationale for providing deliberate mild hypothermia during neurosurgical procedures is provided by a number of laboratory investigations. Busto *et al.* demonstrated that hypothermia to 33°C resulted in a significant decrease in histologic neuronal damage as and in excitatory neurotransmitter release in a rat model of global ischemia.[6,10] Kader *et al.* documented a reduction in histologic damage in a rat model of permanent focal ischemia in animals maintained at 34.5°C during ischemia.[8] Leonov *et al.* demonstrated both improved neurologic outcome and decreased neuronal histologic damage in a dog model of global ischemia at 34°C.[11] In addition, Chopp *et al.* showed a reduction in histologic damage from global ischemia in a rat model when mild hypothermia (to 34°C) was instituted immediately after an ischemic insult.[12] Sano *et al.* have recently shown marked improvement in histologic outcome after decreasing temperature to 35°C when comparing halothane and isoflurane anesthetized normothermic control animals.[7] In fact, modest temperature reduction may be more important than choice of anesthesia as a determinant of outcome from cerebral ischemia.[13]

Mild unintentional hypothermia may be difficult to *avoid* in the perioperative period. Vaughan reported that 60% of adult postsurgical patients had a temperature of <36°C and 13% had a temperature < 35°C on admission to the postanesthesia care unit.[14] Because unintentional hypothermia after general anesthesia is so prevalent, the deliberate institution of mild hypothermia for cerebral protection should be relatively easy. In fact, some neurosurgical centers have begun routinely using hypothermia during operations involving temporary cerebral vascular occlusion and other cerebrovascular procedures incurring a high risk of ischemic injury.[9] An unofficial survey recently conducted regarding neuroanesthetic practice during aneurysm clipping suggested that approximately 70% of the 65 respondents are using some form of deliberate or passive hypothermia.#

Unfortunately, even mild degrees of hypothermia are not without potential risk. Passive rewarming is associated with peripheral vasoconstriction, shivering, and subsequent increases in O_2 consumption and myocardial work.[15,16] Frank *et al.* recently found that postoperative hypothermia (<35°C) was complicated by increased rates of myocardial ischemia, angina, and arterial hypoxemia in a population at risk for coronary artery disease.[17] In addition, a prolonged postoperative temperature of <36.1°C has been correlated with an increase in mortality in the general surgery population.[18] Pharmacokinetics and pharmacodynamics are also adversely affected. Mild hypothermia potentiates bupivacaine-induced ventricular arrhythmias[19] and

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drug metabolism is decreased, thus prolonging the effect of even short-acting drugs.[20,21] Mild hypothermia also increases susceptibility to infection.[22] Moderate hypothermia has other well documented effects, including hypocoagulability, thrombocytopenia, impaired platelet aggregation, and activation of fibrinolysis, all of which reverse with rewarming.[23–25]

Most of these adverse effects have been observed in patients leaving the operating room while still hypothermic. It is unclear whether the potential benefits of cerebral protection gained from mild hypothermia and partial rewarming are offset by the systemic physiologic stress induced, particularly if shivering occurs upon emergence.

Our findings indicate that patients under general anesthesia can easily be cooled at an average rate of 1.0°C/h with a water blanket and a convective device circulating room air in a cool operating room. Active cooling was stopped at a temperature of 35°C, and patients continued to drift downward to a mean temperature of 34.3°C despite the initiation of active rewarming at a temperature of 34.5°C. As a result, temperatures associated with cerebral protection were easily achieved. Initial inadvertent temperature decreases in the normothermic group during anesthetic induction and surgical positioning were difficult to prevent. Sessler *et al.* have shown the decrease in core temperature after anesthetic induction is due primarily to redistribution of body heat to the periphery and not solely a result of increased environmental losses from anesthetic-induced vasodilation.[26] In addition, isoflurane, halothane, and fentanyl–N_2O anesthetics decrease the threshold temperatures at which compensatory peripheral vasoconstriction is initiated.[27–29]

Rewarming was achieved at an average rate of 0.7°C/h, although actual rates varied considerably from 0.1–1.8°C/h and were inversely related to body surface area and weight. Complete intraoperative rewarming proved to be difficult despite aggressive manipulations of the convective heating device and water blanket. The hypothermic patients arrived in the intensive care unit with an average temperature of 35.8°C, and at the rate of rewarming observed, an additional 2.6 h of anesthesia would have been required to attain a core body temperature of 37°C. However, 2 h postoperatively there was no significant difference in temperature between the normothermic and hypothermic groups. Also, the arrival temperature was above the 35°C cardiac ischemic threshold suggested by Frank *et al.*[17]

It was surprising that complete rewarming could not be achieved. Convective heating devices are currently the most effective means of peripherally rewarming a patient[30] and advances in this technology may improve intraoperative warming rates and decrease the time required to return to normothermia. Heated humidification of inspired gases has little effect on intraoperative temperature,[31] and the administration of a limited amount of heated fluids would not add to warming appreciably. Convective warming therapy could always be continued into the postoperative period, and further studies are needed to determine if the administration of a vasodilator during rewarming would hasten the return to normothermia.

There was a disturbing trend, significant at 12 h, for the patients in both groups to become hyperthermic postoperatively. Although the clinical significance of a 0.3°C temperature increase is unclear, mild hyperthermia has been shown to increase ischemic infarct volume and edema in animal models.[32,33] This effect is observed even when the initiation of the hyperthermia is delayed.[32] It is possible that postoperative hyperthermia may negate any benefit derived from deliberate intraoperative hypothermia. Although the temperature increase was small, continued careful monitoring and control of perioperative temperature for all patients at risk for cerebral ischemia appears warranted.

Tympanic membrane temperature was used to reflect brain temperature in this study. Lanier *et al.* demonstrated in dogs that tympanic temperature is, on average, 0.3°C lower than pulmonary artery temperature, which in turn is 0.2°C lower than frontal cortex temperature at a depth of 1 cm.[34] Active cooling and rewarming increased the disparity among the measurements. Little data exists on the effect of systemic temperature changes, ambient temperature, and irrigation on the brain temperature during procedures requiring an open calvarium. Further investigation is necessary to determine the effect of cooling and rewarming therapy on temperature gradients between measurement sites in humans. Tympanic membrane and esophageal temperatures correlated well in our sample ($r = 0.95$), as has been shown in other studies.[35] For this reason esophageal temperatures were substituted during tympanic membrane probe failure.

There are limitations of this study. The degree of hypothermia achieved (34.3°C) was intentionally very mild. The sample size was small; the patients were relatively young and without known coronary disease. Thus, the lack of documented adverse cardiac events

is not surprising. More extensive studies to determine the potential risks of deliberate mild hypothermia in an older (and presumably sicker) population must be completed. Although ideal randomization was not achieved and the surgical team was not blinded to the treatment group, the major outcome variable in this preliminary experiment (temperature) should not have been adversely affected by this element of bias. Further studies of outcome, however, will require strict randomization and blinding methods. The results of future trials to determine the benefit of this therapy must be carefully weighed against a realistic assessment of the risks involved.

In conclusion, although deliberate mild hypothermia during craniotomy is feasible, complete rewarming may be difficult to achieve with current methods and may be followed by shivering and a very small degree of rebound hyperthermia. Careful temperature manipulation in the perioperative period should allow maximal neurologic benefit with minimal detriment to systemic physiology.

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References

1. Solomon RA, Smith CR, Raps EC, Young WL, Stone JG, Fink ME: Deep hypothermic circulatory arrest for the management of complex anterior and posterior circulation aneurysms. Neurosurgery 29:732–738, 1991

2. Chyatte D, Elefteriades J, Kim B: Profound hypothermia and circulatory arrest for aneurysm surgery. J Neurosurg 70:489–491, 1989

3. Spetzler RF, Hadley MN, Rigamonti D, Carter LP, Raudzens PA, Shedd SA, Wilkinson E: Aneurysms of the basilar artery treated with circulatory arrest, hypothermia, and barbiturate cerebral protection. J Neurosurg 68:868–879, 1988

4. Rosomoff HL: Hypothermia and cerebral vascular lesions: I. Experimental interruption of the middle cerebral artery during hypothermia. J Neurosurg 13:332–343, 1956

5. Lougheed WM, Sweet WH, White JC, Brewster WR: The use of hypothermia in surgical treatment of cerebral vascular lesions: A preliminary report. J Neurosurg 12:240–255, 1955

6. Busto R, Dietrich WD, Globus MY-T, Valdes I, Scheinberg P, Ginsberg MD: Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7:729–738, 1987

7. Sano T, Drummond JC, Patel PM, Grafe MR, Watson JC, Cole DJ: A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat. ANESTHESIOLOGY 76:221–228, 1992

8. Kader A, Brisman MH, Maraire N, Huh J-T, Solomon RA: The effect of mild hypothermia on permanent focal ischemia in the rat. Neurosurgery 31:1056–1061, 1992

9. Ogilvy CS, Rich C, Crowell RM: Mild hypothermia, mannitol, and induced hypertension for cerebral protection during temporary vessel occlusion in aneurysm surgery is safe and effective (abstract). J Neurosurg 78:367A (abstract 837), 1993

10. Busto R, Globus MY-T, Dietrich WD, Martinez E, Valdes I, Ginsberg MD: Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20:904–910, 1989

11. Leonov Y, Sterz F, Safar P, Radovsky A, Oku K-I, Tisherman S, Stezoski SW: Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab 10:57–70, 1990

12. Chopp M, Chen H, Dereski MO, Garcia JH: Mild hypothermic intervention after graded ischemic stress in rats. Stroke 22:37–43, 1991

13. Todd MM, Warner DS: A comfortable hypothesis reevaluated: Cerebral metabolic depression and brain protection during ischemia (editorial). ANESTHESIOLOGY 76:161–164, 1992

14. Vaughan MS, Vaughan RW, Cork RC: Postoperative hypothermia in adults: Relationship of age, anesthesia, and shivering to rewarming. Anesth Analg 60:746–751, 1981

15. Michenfelder JD, Uihlein A, Daw EF, Theye RA: Moderate hypothermia in man: Haemodynamic and metabolic effects. Br J Anaesth 37:738–745, 1965

16. Roe CF, Goldberg MJ, Blair CS, Kinney JM: The influence of body temperature on early postoperative oxygen consumption. Surgery 60:85–92, 1966

17. Frank SM, Beattie C, Christopherson R, Norris EJ, Perler BA, Williams GM, Gottlieb SO, the Perioperative Ischemia Randomized Anesthesia Trial Study Group: Unintentional hypothermia is associated with postoperative myocardial ischemia. ANESTHESIOLOGY 78:468–476, 1993

18. Slotman GJ, Jed EH, Burchard KW: Adverse effects of hypothermia in postoperative patients. Am J Surg 149:495–501, 1985

19. Freysz M, Timour Q, Mazze RI, Bertrix L, Cohen S, Samii K, Faucon G: Potentiation by mild hypothermia of ventricular conduction disturbances and reentrant arrhythmias induced by bupivacaine in dogs. ANESTHESIOLOGY 70:799–804, 1989

20. Heier T, Caldwell JE, Sessler DI, Miller RD: Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide—isoflurane anesthesia in humans. ANESTHESIOLOGY 74:815–819, 1991

21. Leslie K, Sessler DI, Bjorksten AR, Moayeri A: Mild hypothermia prolongs the duration of action of atracurium (abstract). ANESTHESIOLOGY 79:A930, 1993

22. Sheffield CW, Sessler DI, Hunt TK: Mild hypothermia during anesthesia decreases resistance to *S. aureus* dermal infection (abstract). ANESTHESIOLOGY 77:A1106, 1992

23. Rohrer MJ, Natale AM: Effect of hypothermia on the coagulation cascade. Crit Care Med 20:1402–1405, 1992

24. Yoshihara H, Yamamoto T, Mihara H: Changes in coagulation and fibrinolysis occurring in dogs during hypothermia. Thromb Res 37:503–512, 1985

25. Valeri CR, Cassidy G, Khuri S, Feingold H, Ragno G, Altschule MD: Hypothermia-induced reversible platelet dysfunction. Ann Surg 205:175–181, 1987

26. Sessler DI, McGuire J, Moayeri A, Hynson J: Isoflurane-induced vasodilation minimally increases cutaneous heat loss. ANESTHESIOLOGY 74:226–232, 1991

27. Stoen R, Sessler DI: The thermoregulatory threshold is inversely proportional to isoflurane concentration. ANESTHESIOLOGY 72:822–827, 1990

28. Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ: The thermoregulatory threshold in humans during halothane anesthesia. ANESTHESIOLOGY 68:836–842, 1988

29. Sessler DI, Olofsson CI, Rubinstein EH: The thermoregulatory threshold in humans during nitrous oxide–fentanyl anesthesia. ANESTHESIOLOGY 69:357–364, 1989

30. Lennon RL, Hosking MP, Conover MA, Perkins WJ: Evaluation of a forced-air system for warming hypothermic postoperative patients. Anesth Analg 70:424–427, 1990

31. Hynson JM, Sessler DI: Intraoperative warming therapies: A comparison of three devices. J Clin Anesth 4:194–199, 1992

32. Chen H, Chopp M: Effect of mild hyperthermia on the ischemic infarct volume after middle cerebral artery occlusion in the rat. Neurology 41:1133–1135, 1991

33. Haraldseth O, Gronas T, Southon T, Thommessen L, Borchgrevink G, Jynge P, Gisvold SE, Unsgard G: The effects of brain temperature on temporary global ischaemia in rat brain: A 31-phosphorous NMR spectroscopy study. Acta Anaesthesiol Scand 36:393–399, 1992

34. Lanier WL, Iaizzo PA, Murray MJ: The effects of convective cooling and rewarming on systemic and central nervous system physiology in isoflurane-anesthetized dogs. Resuscitation 23:121–136, 1992

35. Cork RC, Vaughan RW, Humphrey LS: Precision and accuracy of intraoperative temperature monitoring. Anesth Analg 62:211–214, 1983