

Symposium Article

Side Effects of Mild Hypothermia

Armin Schubert

Department of General Anesthesiology, The Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

Summary: Mild hypothermia is increasingly touted as a low risk clinical measure in brain protection. This article reviews potential adverse effects of mild hypothermia by organ system and suggests a risk assessment framework for clinical decision making. **Key Words:** Brain protection—Hypothermia—Complications.

Mild hypothermia (33°–35°C) has been shown to be protective in the laboratory settings of incomplete global ischemia and focal cerebral ischemia. Three human studies suggest that prolonged extraoperative mild hypothermia is associated with better neurologic outcome after head injury (1–3). Mild hypothermia has been proposed for clinical use as an adjunct for achieving protection from cerebral ischemia (4,5). Mild intraoperative hypothermia is currently used for brain protection during aneurysm clipping at several major centers.

The following discussion reviews complications of hypothermic therapy and relates their risk to the potential benefits of mild hypothermia. Induction and maintenance of mild hypothermia are occasionally associated with unintentional further temperature reduction. Accordingly, literature dealing with temperature reduction to 30°C is reviewed.

CIRCULATORY EFFECTS

The circulatory effects of hypothermia include increased peripheral vascular resistance and cardiac afterload (6,7). As cooling proceeds, fluid leaves the vascular space, resulting in mild increases in hematocrit and blood viscosity (8). Hemoconcentration and low microcirculatory flow contribute to the known increase in blood viscosity of 4%–6% for each 1°C in temperature reduction (8). Cold-induced diuresis caused by suppression of antidiuretic hormone (ADH) and shunting of peripheral blood volume centrally leads to further depletion of intravascular volume. The hypothermic patient may therefore be at greater risk for hypovolemia when compared to a normothermic individual, particularly once rewarming is started.

CARDIAC EFFECTS

Hypothermia may be associated with myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial (PIRAT) (9) study group reported a significantly higher (36% vs. 13%) incidence of postoperative myocardial ischemia diagnosed by

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Address correspondence and reprint requests to Dr. Armin Schubert, Chairman, Department of General Anesthesiology/M26, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195-5001, U.S.A.

electrocardiogram (ECG) in vascular surgery patients who arrived in the intensive care unit (ICU) with temperatures $<35^{\circ}\text{C}$, when compared to those who arrived normothermic. Moreover, hypothermic patients had a higher rate of postoperative angina (18% vs. 1.5%), despite similar preoperative risk factors. Mild hypothermia can therefore be expected to predispose to coronary ischemia in susceptible patients.

Hypothermia of $34^{\circ}\text{--}35^{\circ}\text{C}$ markedly decreased porcine left ventricular contractility (10) and neonatal cardiac output (by 39%) (11). Hypothermia also impairs diastolic relaxation. Furthermore, the efficacy of cardiovascular medications may be impaired during mild hypothermia. Dobutamine's salutary effect on contraction velocity of isolated perfused and spontaneously beating rabbit hearts was substantially reduced at 32°C (12). In isolated perfused hearts, a mild inotropism has been demonstrated with mild hypothermia, possibly related to increased myofilament Ca^{2+} responsiveness (13). However, it takes the heart longer to develop maximal strength of contraction and therefore may prevent its conversion into useful work (10). During mild hypothermia, the decrease in myocardial contractility, the augmented negative inotropic effects of volatile anesthetics (14), the lesser cardiac responsiveness to catecholamines (15), and the slower metabolism of anesthetic agents may set the stage for administration of a relative anesthetic overdose by unwary practitioners.

Hypothermia and rewarming can elevate plasma catecholamine levels with the potential attendant problems of cardiac arrhythmias, hypertension, and myocardial ischemia. Mild hypothermia generally is not directly responsible for cardiac arrhythmias but may cause conduction disturbances and ventricular irritability by potentiating other drugs such as bupivacaine (16) or by causing hypokalemia (17). At temperatures below 32°C , there is a tendency to develop atrial fibrillation (18). If mild hypothermia is allowed to drift below 30°C , spontaneous ventricular fibrillation may occur (6).

Mild hypothermia shifts potassium intracellularly and predisposes to hypokalemia with related cardiac complications in postsurgical patients (17). As well, the toxicity of potassium administration appears to be potentiated by hypothermia. Sprung et al. (19) observed that the rat cardiac toxicity of intravenously administered potassium progressively

increased with falling temperature. At 31°C , toxicity was 5% higher than at 37°C . Aggressive potassium replacement during hypothermia can furthermore result in hyperkalemia on rewarming (20).

Nonuniform cooling or rewarming of the heart may cause regional heterogeneity of conduction, action potential duration, and refractory periods. This in turn favors unidirectional conduction block and reentrant dysrhythmias (21), seen with moderate (22) and mild (23,24) hypothermia.

PULMONARY EFFECTS

Mild hypothermia may contribute to pulmonary abnormalities in the postoperative period. Signs of pulmonary edema have been described upon rewarming from mild hypothermia in brain tumor patients (25) and after environmental exposure (26) and have been attributed to a central mechanism. Patients who arrived in the ICU with a temperature $<35^{\circ}\text{C}$ after peripheral vascular surgery were more likely to have marginal oxygenation ($\text{PaO}_2 < 80$ mm Hg) than those who arrived with normal temperature (9). Recently, Bissonette and Sessler (27) reported no adverse effects of core temperatures between 34°C and 36°C on the postanesthetic recovery of children. While at first this report may appear reassuring, it must be remembered that few would consider 36°C mild hypothermia for brain protective purposes. Furthermore, the patients studied by these investigators underwent peripheral surgery which lasted no longer than 3 h. This is substantially different from the population of patients who might most benefit from mild hypothermic intraoperative management.

The increased metabolic demand after naloxone reversal of opioid drugs has been associated with myocardial ischemia and pulmonary edema. Just et al. (28) demonstrated that mild hypothermia (34.2°C) potentiates the increase in minute ventilation and oxygen uptake (VO_2), which occurs after naloxone reversal. An increase in VO_2 of 114% was observed in hypothermic patients, compared to an increase of only 25% in normothermic (36.8°C) patients.

NEUROLOGIC EFFECTS

The cerebral effects of hypothermia are well known and will not be repeated here. Rather, this

section emphasizes potential adverse effects. With each degree of temperature reduction, cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂) decrease approximately 5% (29). However, at 29°C, CBF distribution was inhomogeneous in monkeys and failed to return to baseline (30). Steen et al. (31) further observed cardiovascular collapse with severe hypoxia and acidosis on rewarming similarly cooled dogs. While these effects were observed at a substantially lower temperature than what is meant by mild hypothermia, they are still of concern since hypothermic overshoot can develop after induction of mild hypothermia, especially in patients with central nervous system (CNS) injury (Clifton, personal communication, 1994).

In halothane-anesthetized rats, CBF autoregulation during hypothermia to 30.5°C was either impaired or abolished, depending on CO₂ management (32). Temperature also affects the reactivity of isolated perfused cerebral arterioles. Progressive hypothermia leads to calcium-dependent vasodilation (33).

Rewarming after mild hypothermia may present the greatest challenge to the CNS. Rebound increases in intracranial pressure (ICP) and hyperthermic overshoot are of concern. While no ICP rebound was recorded by Marion et al. (3), their hypothermic patient group did require more therapeutic interventions to control ICP than their normothermic controls. Baker et al. (34) found, however, that patients treated with mild intraoperative hypothermia had higher late postoperative temperatures than normothermically treated controls. The significance of this finding is unclear but of concern, given the known deleterious sequelae of hyperthermia to tissue recovering from ischemia (35).

COAGULATION SYSTEM EFFECTS

Hypothermia-induced coagulation abnormalities include reversible platelet sequestration and dysfunction, enhanced fibrinolytic activity, and slowing of enzymatic activity required for clotting (36).

Temperature affects prothrombin time (PT), thrombin time (TT), and partial thromboplastin time (PTT) (37). At 34°C, PT and PTT increased by 9% compared to 37°C (38). It should be noted, however, that clinical laboratories routinely perform clotting tests at 37°C. Assessment of clotting factor

levels by measuring PT and PTT at 37°C does not adequately describe the hypothermic coagulation defect. This is because hypothermia interferes with the enzymatic steps in the clotting cascade, independent of clotting factor level (38,39).

Platelet function appears to be adversely affected by mild hypothermia. Surface cooling to 32°C can produce reversible platelet dysfunction (40). In hypothermic (30°C) pigs, Oung et al. (41) found that bleeding time was nearly doubled. In neonatal cold injury, however, rewarming deaths are attributed to hyperaggregation of platelets and resultant massive hemorrhage (42). Thrombocytopenia has only rarely been reported in environment-induced mild hypothermia (43). Mild to moderate hypothermia has been implicated in exacerbating perioperative coagulopathy, particularly in severe injury (44). Eighty percent of nonsurviving trauma patients were hypothermic compared to 36% of survivors (45). Nonsurvivors were more severely hypothermic ($31.0 \pm 1.0^\circ\text{C}$ vs. $34.0 \pm 0.5^\circ\text{C}$) and developed clinically significant bleeding despite adequate blood component replacement when compared to survivors. While 31°C would not normally be attained during mild hypothermic techniques for brain protection, unanticipated major blood loss, after-drop effects, and equipment malfunction might well combine to precipitate this complication. During exploratory laparotomy in trauma patients, blood loss was significantly larger in patients with temperatures of 33–35°C, independent of the severity of injury, when compared to patients whose temperatures were maintained above 35°C (46). Studies relating temperature to surgical blood loss are difficult to interpret, however, since the massive transfusion itself can be a factor in the development or exacerbation of hypothermia (47).

The integrity of the coagulation system is particularly important during and after intracranial surgery, as hemostatic control can be somewhat tenuous. Coagulopathy predisposes to intracranial bleeding (48) and postoperative intracranial hemorrhage is associated with poor outcome and severely prolonged hospital stay (49).

METABOLIC EFFECTS

Decreasing body temperature lowers metabolic rate by approximately 5%–7% per °C (6,7). Hypothermia also shifts the hemoglobin–oxygen dissoci-

ation curve to the left, thus reducing tissue oxygen availability. This may contribute to an uncompensated metabolic acidosis (17), which is commonly observed with hypothermia. A lower metabolic rate is associated with decreased CO₂ production, which promotes a respiratory alkalosis when minute ventilation is unchanged, as often occurs in the operative setting.

Metabolism of anesthetics and muscle relaxants (50) is slowed during mild intraoperative hypothermia. Hypothermia of 34°C during recovery from incomplete spinal cord injury was associated with toxic plasma levels of phenytoin, suggesting that mild hypothermia affects the metabolism of this drug sufficiently to warrant clinical concern (51). Citrate metabolism decreases 30%–40% between 37° and 30°C (52). Mild hypothermia may therefore hasten the development of citrate toxicity during transfusion. Mild intraoperative hypothermia also appears to compound the tendency for protein breakdown and nitrogen loss after major orthopedic (53) and abdominal (54) surgery.

IMMUNOLOGIC/HORMONAL EFFECTS

Leukocyte mobility and phagocytosis are modestly impaired during mild hypothermia (55). Reversible pancytopenia has been described in association with moderate hypothermia of 31.1°C (56). Mild hypothermia under halothane anesthesia led to increased bacterial counts and a larger area of induration after a standard bacterial dermal inoculum (57). Immunologic depression combined with decreased cutaneous blood flow during mild hypothermia (58) and surgical manipulations may therefore increase the risk of wound infection. Immune suppression associated with hypothermia may thus account for the trend toward higher sepsis and pneumonia rates in recent trials employing mild hypothermia for closed head injury.

In the awake state, mild hypothermia induces a number of hormonal changes, such as an increase in plasma corticosterone and thyroid-stimulating hormone (TSH), a decrease in plasma prolactin, and a decrease in hypothalamic thyrotropin-releasing hormone (TRH). It is suggested that mild hypothermia causes prolactin release through a central dopaminergic mechanism and that the increased TSH levels are due to release of TRH (59,60). These findings indicate that mild hypothermia is associated

with widespread physiologic alterations, the full extent and implications of which have yet to be defined.

INTERFERENCE WITH INTERPRETATION OF DIAGNOSTIC TESTS OR MONITORS

Twenty-four-hour holter monitoring of poikilothermic patients showed mild hypothermia (33.9°C) to be associated with a reduction in heart rate, a prolongation of the Q-T interval, and an increase in short-term heart rate variability (23,61). These changes are the result of slowed myocardial conduction, a decrease in the resting membrane potential, and prolongation of the action potential and refractory period (21). At a rectal temperature of 33.6°C, the ECG may mimic acute myocardial infarction (62).

Monitoring neuromuscular blockade by compound electromyogram may be more misleading during mild to moderate hypothermia, compared with monitoring mechanical twitch tension (63). Furthermore, mild hypothermia to 31.9°C markedly prolonged the rate at which serum concentration of d-tubocurarine and twitch tension equilibrated, resulting in an apparent marked delay in onset of paralysis which could be interpreted as decreased sensitivity. Hypothermia also itself decreases the adductor pollicis twitch response, prompting the recommendation to maintain the temperature of this muscle above 35°C (64) for optimal monitoring of neuromuscular block.

Hypothermia reduces carbon dioxide production and may lead to excessive respiratory alkalosis if appropriate ventilatory adjustments are not made. Furthermore, owing to altered gas solubilities, blood gas tensions and pH are affected by hypothermia, although the clinical significance of these changes is controversial. With each °C decrease, pH increases by 0.015, PCO₂ decreases by 4.4%, and PO₂ decreases by 7.2% (6). Misinterpretation of "corrected" blood gas results may result in relative brain tissue acidosis and abolition of CBF autoregulation.

In mildly hypothermic surgical patients, conventional finger pulse oximetry was less successful (18% failure rate) and reliable than pulse oximetry of the nasal septum, which was successful in all 50 estimations (65). An alternative to finger pulse ox-

imetry should therefore be considered during hypothermic techniques.

Mild hypothermia slightly prolongs the latency of somatosensory (SSEPs) (66,67) and corticomotor evoked potentials (CMEPs) (66). Amplitude of SSEPs is variably affected in the range of 32°–36°C, while CMEP amplitude increases with decreasing temperature. Brainstem auditory evoked potential (BAEP) latency increases with hypothermia, but mild hypothermia does not interfere with BAEP monitoring. Hypothermia to 33.5°C causes the electroencephalogram (EEG) to shift toward theta and beta frequencies and reduces the alpha frequency component (68). Total EEG power and peak EEG frequency appear to be linearly related to core temperature (69). While there are definitive effects of mild hypothermia on evoked potentials and EEG, they may be expected to interfere only rarely with proper interpretation.

REWARMING CONSIDERATIONS

Vigorous peripheral rewarming of hypothermic patients is known to lead to a decrease in central temperature, which may be responsible for the ventricular fibrillation and cardiovascular collapse occasionally observed in victims rewarmed from accidental hypothermia. Fortunately, this temperature afterdrop is small during rapid peripheral rewarming from mild hypothermia (70) but can still be associated with moderate decreases in blood pressure and peripheral vascular resistance (71).

Rewarming after mild hypothermia generally takes place at a brisk pace in the operative setting so that near-normothermic conditions can be achieved at the time of emergence from anesthesia. The most widely employed methods to reverse mild hypothermia rely on peripheral warming, such as warming the ambient temperature and through the use of convective warming devices. Peripheral rewarming from mild hypothermia is also associated with the afterdrop phenomenon, originally described with rewarming from more severe hypothermic states. Core temperature continues to decrease for approximately 30 min after peripheral rewarming from mild hypothermia (72). The magnitude of this afterdrop was about 0.6°C. If hypothermia is rapidly reversed without proper monitoring of and attention to this phenomenon, patients may be recovered at a lower core temperature than the

intraoperative target, with resultant potentially dangerous consequences. Our clinical experience indicates that a hypothermic "overshoot" of ~0.5–0.7°C can readily occur after peripheral cooling to mildly hyperthermic temperature.

Thermoregulatory vasoconstriction normally limits heat transfer between body compartments. The efficacy of forced-air warming in reversing hypothermic core temperature may therefore be limited (73) until thermoregulatory vasoconstriction ceases. Patients rendered hypothermic intraoperatively, even to a mild degree, appear to be at higher risk for postoperative hypothermia. This is likely due to the fact that the critical surgical intervention associated with the risk of cerebral ischemia occurs toward the end of a long case. Even with special equipment, it is relatively difficult to rewarm cold patients quickly in an operating room environment (73,74). The rate of intraoperative surface rewarming is approximately 0.7°C/h and depends inversely on body surface area (BSA). Despite active peripheral rewarming measures after therapeutic intraoperative mild hypothermia, Baker et al.'s (34) hypothermic patients still had a significantly lower body temperature on arrival to ICU when compared to the normothermic group (35.8 vs. 37.1°C). Approximately 10–12 h thereafter, hypothermic patients were actually slightly hyperthermic when compared to patients who were kept at normal temperature intraoperatively. This finding has raised some concern as hyperthermia is detrimental to brain tissue recovering from ischemic injury (35).

Accepted warming devices include electrically heated humidified breathing circuits, fluid warmers, electrical and circulating water warming blankets, convective forced-air warmers, and infrared heating lamps. These devices have all been associated with complications primarily consisting of burns and skin irritation. Inasmuch as intraoperative mild hypothermic techniques require rapid rewarming, these devices may present a certain hazard even in the hands of experienced personnel.

Postoperative hypothermia frequently causes thermoregulatory shivering. Core temperature at the end of surgery is the most important determinant for the occurrence of postoperative shivering (75). Between 33.5° and 36.5°C, a decrease by 1°C increased the probability of shivering by 33%. The associated higher myocardial oxygen demand may induce myocardial ischemia in susceptible patients.

Metabolic activation from shivering can also result in the development of respiratory acidosis (76) as well as increased tissue oxygen extraction (77) and resulting systemic hypoxemia and metabolic acidosis. Shivering also increases patient discomfort and leads to more aggressive medication with muscle relaxants (78), antihypertensives, analgesics, and sedatives. It increases intraocular pressure (79); strains surgical repairs (80); and impedes blood pressure, ECG, and pulse oximetry monitoring.

EXCESSIVE HYPOTHERMIA

Thermoregulatory vasoconstriction normally limits the degree of mild hypothermia to about 34°C even in neurologically intact anesthetized patients. However, this may not necessarily be the case in patients undergoing craniotomy or those with traumatic head injury (1) perhaps because of a central impairment of the thermoregulatory response. Unintentionally more severe hypothermia may also result from failure to monitor core temperature and from failure to account for the factors which influence cooling rates. In addition, sudden major hemorrhage and, in the trauma setting, associated vascular injuries and low perfusion states can quickly lower temperature beyond the intended value. The human response to cooling is quite variable and appears to depend on age, gender, and body mass. In the awake state, older men are less able to defend core temperature than younger men. This age difference was not observed in women, however (81). Baker et al. (34) noted a strong correlation between BSA and the rate of intraoperative temperature change.

ADVERSE CLINICAL OUTCOME WITH HYPOTHERMIA

In 100 consecutive noncardiac surgery patients, temperature of <36°C was associated with increased mortality but also with more advanced age, longer duration of surgery, and greater operative fluid requirement (82). Hypothermia is significantly associated with mortality in severely injured trauma patients (45). In another study, hypothermic trauma victims with core temperatures <35°C had a higher mortality than their normothermic counterparts. However, when they were stratified by severity of injury, posttraumatic hypothermia did not appear to exert an independent effect on outcome (83).

Hypothermic patients require more intensive nursing care with more frequent interventions (1) and, as a result, longer recovery room stays (84). In a prospective, randomized trial of mild hypothermia (32°–33°C) for severe closed head injury, Marion et al. (3) found no increase in complications when compared to normothermia. However, upon re-warming, the hypothermic group required more intense therapy to keep ICP at the same level as the normothermic group. Hypothermia established at 32°–33°C and maintained for 48 h in closed head injury may have been associated with a higher rate of sepsis (1).

The argument has been made that mild hypothermia causes relatively modest physiologic disturbances, which are reversible and ultimately have no influence on patient outcome. Of concern, however, are a number of reports which link mild or moderate hypothermia to increased mortality in trauma (85–87) and postoperative surgical intensive care (82). While occurrence of hypothermia in these reports may well have represented only a marker of severity of injury or illness, the data certainly do not inspire extreme confidence in the safety of hypothermia. Answers regarding the clinical significance of hypothermia-related complications remain vague, but the accumulated evidence speaks against mild hypothermia being a reliably innocuous intervention. Even if the technique were proven to be free of complications in expert hands, the potential for harm still exists. If embraced too hastily, it may develop undesirable popularity with less than qualified personnel, who may be further handicapped by inadequate technical and ancillary support.

RISK ASSESSMENT AND PRECAUTIONS

The ability to identify risk factors for mild hypothermia-related complications should be useful to all clinicians managing patients at high risk for neurologic injury, be it in the operating room or in the ICU. In the trauma patient, aortic clamping, large volume fluid resuscitation, metabolic acidosis, and hypothermia are said to be mutually reinforcing risk factors for perioperative circulatory collapse (45,44). In a cohort of 97 vascular surgery patients, Frank et al. (88) have identified advancing age (>60 years), cold operating room temperature, and general anesthesia (vs. epidural), but not duration of surgery or extent of intravenous fluid administra-

TABLE 1. Risk considerations for clinical decision making regarding mild hypothermia

a. Minimal risk	Younger patients (<60 years) without coronary disease Normal coagulation and immune status
b. Mildly increased risk	Low probability of massive fluid resuscitation Predisposition to coronary artery disease Patients with low BSA Need for major fluid resuscitation Older patients (>60 years)
c. Moderately increased risk	Immune suppression Definitive diagnosis of coronary artery disease Reversal of opioid effect in mildly hypothermic patients with documented moderate/severe coronary disease Baseline coagulopathy Inadequate technical resources or personnel trained in the prevention and treatment of hypothermic complications
d. Contraindications	Cryoglobulinemia; other cold-induced disease

BSA, body surface area.

tion, as risk factors for the development of intraoperative mild hypothermia. Advancing age was found to increase rewarming time in the recovery room.

An intermediate step toward risk assessment for mild hypothermia is the identification of conditions which predispose to its rapid development and, possibly, hypothermic overshoot. Furthermore, adverse physiologic consequences of mild hypothermia may combine to add risk if imposed on patients with functional impairments in body systems affected by hypothermia. To complete a risk assessment matrix, disease states known to be associated with complications after mild hypothermia should be considered. The schema in Table 1 gives a framework for clinical reasoning in the decision to institute mild hypothermia. Until the clinical benefits of mild hypothermia are more clearly delineated, a careful consideration of its adverse effects should enter into any decision to employ this technique for protection of CNS components at risk. Many of the risk factors can undoubtedly be neutralized by a highly organized and experienced team of anesthesiologists, intensivists, and surgeons. However, the individual patient can be sufficiently complex as to warrant careful considerations of all risks and benefits. Mild hypothermia is easily achieved, is widely prevalent in operating rooms, and as yet has not been proven to carry excessive risk. These are not, however, sufficiently compelling reasons to expand its use routinely to all patients at risk for neurologic injury.

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