Defeating Normal Thermoregulatory Defenses
Induction of Therapeutic Hypothermia

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Abstract—Therapeutic hypothermia may be useful in various circumstances including stroke. However, core body temperature is normally tightly regulated. Even mild hypothermia in conscious subjects thus provokes vigorous thermoregulatory defenses which are potentially harmful in fragile patients. Furthermore, thermoregulatory responses are effective, which reduces the rate at which hypothermia can be induced. Drugs are thus often given to blunt normal thermoregulatory defenses. General anesthetics profoundly impair thermoregulatory control, but prolonged general anesthesia is rarely practical or appropriate. A variety of other drugs have therefore been evaluated. Most opioids only slightly impair thermoregulatory defenses, but meperidine is considerably more effective than equipotent doses of other opioids. The central α2 agonists clonidine and dexmedetomidine are also useful. However, the best overall approach to inducing thermal tolerance appears to be a combination of buspirone and meperidine, which reduces the core temperature triggering shivering to about 33.5°C in doses that maintain adequate ventilation. (Stroke. 2009;40:e614-e621.)

Key Words: anesthesia ■ thermal tolerance ■ temperature ■ hypothermia ■ brain protection

Overwhelming evidence in animals indicates that even mild hypothermia provides substantial protection against ischemia. Large randomized trials have shown that mild hypothermia protects humans after cardiac arrest and neonatal asphyxia. Uncontrolled studies suggest that hypothermia may be useful in other circumstances, including stroke.

Various cooling devices are already available, and new ones are in development. But perhaps the major difficulty with induction of therapeutic hypothermia is that even mild hypothermia in conscious subjects provokes vigorous thermoregulatory defenses, particularly vasoconstriction and shivering. Not only do vasoconstriction and shivering slow onset of hypothermia, but they are associated with hypertension, tachycardia, and sympathetic nervous system activation—all of which are potentially harmful in fragile patients.

Unless physicians are willing to let their patients tolerate considerable hemodynamic stress and autonomic activation, cooling of conscious patients must be accompanied by induction of thermal tolerance. Although physical methods have been proposed to trick the thermoregulatory system into permitting hypothermia, the most practical approach is to use various drugs or drug combinations to blunt normal thermoregulatory defenses. I will thus review pharmacological methods for inducing enough thermal tolerance to permit induction of mild therapeutic hypothermia without activating excessive thermoregulatory defenses.

Potential Benefits of Therapeutic Hypothermia

Hypothermia reduces metabolic rate of tissues by approximately 8% per °C.1 Hypothermic protection against ischemia was initially attributed to reduced tissue metabolism. However, the efficacy of mild hypothermia far exceeds that of treatments such as high-dose isoflurane or barbiturate coma, which comparably reduce the metabolic rate. It is most likely that other actions (eg, decreased release of excitatory amino acids, reduced inflammation) explain the protective action of hypothermia.2 It appears that much of the total benefit from moderate hypothermia occurs within the first couple of degrees,3 thereby making hypothermia an attractive therapeutic option because the benefits may well exceed the risks.

There is in vitro2 and overwhelming animal4 evidence that mild hypothermia provides substantial protection against tissue ischemia. Although the amount of protection varies with the model, several degrees of hypothermia typically provide factor-of-three benefits. In fact, just a couple °C hypothermia provides better protection against ischemia than any known drug. Most work has focused on the brain, but there is evidence that benefit extends to other tissues, most notably the heart (Figure 1).5 There has thus been considerable interest in using mild hypothermia therapeutically.

Unfortunately, therapeutic hypothermia has proven harder to document in humans than animals. Several factors contribute, but one of the most important is that ischemia can rarely be anticipated in humans. Hypothermia is therefore usually induced after onset of ischemia when much irreparable tissue damage has already occurred.
damage has already occurred. In practice, it often takes 3 hours or longer before cooling can even start. And once started, it can easily take several additional hours to induce hypothermia because humans have so much more mass than most experimental animals. The intervention window remains unknown in humans, but animal studies suggest that it is not likely to be more than a few hours.2

Although any number of observational studies suggest that therapeutic hypothermia (or fever prevention) may be helpful, limited prospective data support this theory. There are nonetheless 2 circumstances in which large randomized trials have proven mild hypothermia to be beneficial in humans. The first is in asphyxiated neonates.4,5 It is easy to cool infants—in fact, the difficulty is usually preventing hypothermia. Mild hypothermia is thus rapidly being adapted as the therapeutic choice for asphyxiated neonates.

The second circumstance is in out-of-hospital cardiac arrest. Two studies, one from Austria6 and the other from Australia,6 report that hypothermia to 32 to 34°C improves long-term neurological outcome in arrest survivors. In the first, the chances of a favorable neurological outcome increased from 39% to 55%; in the second, survival with favorable outcome increased from 26% to 49%. This results is all the more impressive because in one of the studies,6 core temperature took 8 hours to reach 34°C.

In contrast, large randomized trials of therapeutic hypothermia have failed to demonstrate a convincing benefit for brain trauma,7 cerebral aneurysm repair,8 or acute myocardial infarction. And although a preliminary trial was encouraging, a full-scale randomized trial of therapeutic hypothermia for stroke has yet to be reported. Major clinical trials of therapeutic hypothermia are listed in the Table. A recent book reviews the topic in detail.9

Although not the purpose of this review, it is worth noting that mild perioperative hypothermia is associated with numerous severe complications, including morbid myocardial outcomes, surgical wound infection, coagulopathy, prolonged recovery, and prolonged hospitalization. The consequences of perioperative hypothermia have been reviewed in detail.10 Patients made hypothermic therapeutically are, at the very least, at increased risk for infection and coagulopathy, and infection is a frequent complication in patients kept hypothermic for prolonged periods.

### Normal Thermoregulation

Thermoregulation is a primitive and powerful homeostatic system that is usually well maintained even in patients with serious illness, including acute stroke.11 Roughly speaking, thermoregulation is a conventional feedback system with afferent input into a central control system that in turn

![Image](http://stroke.ahajournals.org/)

**Figure 1.** The left anterior descending coronary artery was occluded for 60 minutes, followed by reperfusion for 3 hours in open-chest pigs. Core body temperature was either reduced to 34°C starting 20 minutes after occlusion and maintained for 15 minutes after reperfusion (n=6), or maintained at 38°C (n=6). Infarct size normalized as a percent of the area at risk. Open and closed circles indicate individual experiments and group means respectively. Hypothermia was highly protective. AAR is area at risk. Adapted from Dae et al.5
activates efferent defenses. Core temperature is normally more tightly regulated than other homeostatic systems such as blood pressure and vascular volume, thus indicating the premium mammals place on normothermia.

It is helpful to divide body temperature and heat distribution into core and peripheral tissue compartments. Core temperature is the average temperature of well-perfused deep organs and the neuraxis. The core compartment is thus usually modeled as the trunk and head. Because perfusion is so high, core temperature is nearly homogeneous. In contrast, the arms and legs—roughly half the body mass—are typically 2 to 4°C cooler than the core and there are substantial temperature gradients within the peripheral thermal compartment. Peripheral tissue temperature is not tightly regulated and thus serves as a buffer between the well-protected core and the environment.

Central Control
Thermoregulation can be divided into behavioral and autonomic control. Behavioral control is defined by thermal comfort and volitional responses provoked by feeling excessively warm or cold. Behavioral thermoregulation includes use of protective clothing, building shelter, and air conditioning. It is thus by far the most powerful thermoregulatory defense and is the one that allows humans to prosper in the diverse environments we inhabit.

Core temperature is normally controlled to a daily average of 37°C. Core temperature is controlled by activation of thermoregulatory defenses, which are generally effective and return the core to its designated temperature. The hypothalamus is the dominant controller in humans, although there is substantial integration of thermal input throughout the neuraxis.

A useful thermoregulatory model characterizes responses by their thresholds, defined as the core temperatures triggering each response. The rate at which response intensity increases with further deviation in core temperature defines the gain of the response, which then reaches a maximum response intensity. The temperature difference between the first warm response (sweating) and the first cold defense (vasoconstriction) defines the interthreshold range. Typically, the interthreshold range is only a few tenths of a °C.

The most important autonomic thermoregulatory defenses in humans are sweating and active precapillary vasodilation, arteriovenous shunt vasoconstriction, and shivering. Vasoconstriction is the most commonly used defense, and is often activated numerous times in the course of a day. Although thermoregulatory shunts are essentially restricted to the fingers and toes, they effectively constrain metabolic heat to the core thermal compartment.

Afferent Input
Tissues throughout the body contribute to thermoregulatory control. However, input can roughly be divided into cutaneous and core input. The reasons are that core temperature is homogeneous and that peripheral temperature parallels mean-skin temperature. Mean-skin temperature can be estimated from as few as 4 temperatures.

The contribution of mean-skin temperature to thermoregulatory control depends on the defense. Skin temperature contribute about 10% to control of sweating, but about 20% to control of vasoconstriction and shivering (Figure 2). Autonomic responses are thus based largely on core rather than skin temperature. Nonetheless, each 4°C increase in mean-skin temperature reduces the thresholds for vasoconstriction and shivering by 1°C. Behavioral responses differ in being far more sensitive to skin temperature; 50% of thermal comfort is determined by skin temperature. Because core temperature is usually nearly constant, how humans feel about their thermal environment is thus largely determined by skin temperature.

Thermoregulation Impedes Induction of Therapeutic Hypothermia
Induction of therapeutic hypothermia is relatively easy in patients who are anesthetized because general anesthesia profoundly impairs thermoregulatory defenses. Similarly, thermoregulatory defenses are often blunted in deeply unconscious patients. But in relatively intact patients (including those with strokes), hypothermia provokes vasoconstriction and shivering, both of which are problematic.

Hypothermia invokes arteriovenous shunt constriction. The difficulty is that shunt constriction, which normally restricts flow of metabolic heat from the core to peripheral tissues (presumably, its evolutionary purpose), equally well limits the efficacy of surface cooling by effectively isolating core tissues from the periphery. It also causes hypertension (Figure 3).

In additional to arteriovenous shunt constriction, moderate hypothermia provokes a 3-fold increase in circulating catecholamine concentrations. These catecholamines cause systemic vasoconstriction that further reduces peripheral perfusion and, consequently, increases thermal isolation of core and peripheral tissues. Surface warming and cooling is thus more effective during anesthesia (when patients are relatively vasodilated) than without. Similarly, heat transfer through the legs is enhanced when vasodilation is maintained by spinal anesthesia.

Shivering is involuntary, and augments metabolic heat production. The shivering threshold is normally about 35.5°C, about 1°C below the vasoconstriction threshold. Shivering can double metabolic heat production over long
periods. To the extent that shivering increases metabolic rate, it diminishes the efficacy of applied cooling, and thus slows induction of therapeutic hypothermia. Furthermore, shivering is potentially harmful because it is associated with hypertension and sympathetic nervous system activation. Shivering has been reviewed in detail.

Pharmacological Interventions

It is difficult to induce hypothermia without provoking excessive vasoconstriction and (especially) shivering. The most potent inducers of thermoregulatory tolerance are general anesthetics, especially the volatile anesthetics, although anesthesia is not a practical option in most patients. Muscle relaxants do not directly affect thermoregulatory control but do prevent shivering. However, muscle relaxants must be combined with anesthesia or deep sedation and are inappropriate for long-term use in most patients. There is thus considerable interest in drugs and drug combinations that moderate autonomic cold defenses without causing excessive side effects, especially ventilatory compromise.

Anesthetic-Induced Thermal Tolerance

All anesthetics profoundly impair thermoregulatory control. But interestingly, the sweating threshold increases only slightly. In contrast, the thresholds for vasoconstriction and shivering decrease substantially. Dose-dependence is linear with intravenous anesthetics such as propofol, but the thresholds are disproportionately decreased at high doses of volatile anesthetics such as isoflurane and desflurane (Figure 4). In all cases, the vasoconstriction and shivering thresholds are reduced synchronously; that is, the shivering threshold remains almost exactly 1°C less than the vasoconstriction threshold for any anesthetic drug and at any dose.

General anesthetics thus increase the interthreshold range (temperatures not triggering thermoregulatory defenses) by a factor of 10 or more. Once triggered, the gain of vasoconstriction is reduced, but maximum response intensity is preserved during anesthesia. In contrast, the maximum intensity of shivering is reduced.

Because anesthetics so impair thermoregulatory control, it is easy to induce therapeutic hypothermia in anesthetized subjects. In fact, the more common problem is that anesthetic-induced impairment makes surgical patients prone to inadvertent hypothermia—and the associated complications. The effect of coma on thermoregulatory control has not been quantified. Nonetheless, it appears that deep coma, like anesthesia, profoundly impairs thermoregulatory control, thus facilitating induction of therapeutic hypothermia.

Nonanesthetic Drugs

Opioids

Both μ- and κ-opioid receptor agonists impair thermoregulatory control. While causing much less inhibition than intravenous anesthetics such as propofol, the pattern of impairment is similar: they only slightly increase the sweating threshold, but linearly and synchronously reduce the vasoconstriction and shivering thresholds. (Once triggered, the gain and maximum intensity of shivering remains normal during opioid administration.) Meperidine differs from other drugs in disproportionately reducing the shivering threshold; that is, producing a dose-dependent reduction in
The sweating threshold increased as a function of unbound plasma meperidine concentration: Sweating=0.5 (Meperidine ([C] · [μg]⁻¹ · [ml]) + 37.1, r²=0.10. In contrast, meperidine produced a linear decrease in the core temperature triggering vasoconstriction: Vasoconstriction=−3.0 (Meperidine ([C] · [μg]⁻¹ · [ml]) + 36.6, r²=0.54. Meperidine decreased the shivering threshold nearly twice as much as the vasoconstriction threshold. Shivering=−5.6 (Meperidine ([C] · [μg]⁻¹ · [ml]) + 35.6, r²=0.62. Dashed lines indicate 95% confidence intervals. Adapted from Kurz et al.31

The shivering threshold that is twice the reduction in the vasoconstriction threshold (Figure 5).31 Meperidine has numerous pharmacological actions, and 1 or more of these probably accounts for its remarkable antishivering efficacy. The special antishivering action of meperidine might in part be mediated by its agonist activity at κ-receptors. Kappa activity constitutes about 10% of the total opioid action of meperidine. However, nalbuphine turns out to be a relatively poor inhibitor of shivering and does not disproportionately reduce the shivering threshold.32 Meperidine also has central anticholinergic activity; but anticholinergic medications increase the vasoconstriction and shivering thresholds rather than reduce them.32 Another potential explanation for the special antishivering activity of meperidine is a recently described activation of α₂b adrenoceptors.33 This is important because, as noted above, α₂ receptor agonists such as clonidine34 and dexmedetomidine35 synchronously reduce the vasoconstriction and shivering thresholds. The special antishivering action of meperidine may be similarly mediated.

But the special antishivering effect of meperidine could equally well result from a yet-to-be-determined aspect of the pharmacology of the drug—or from a combination of factors. For example, unlike other opioids, meperidine produces generalized electroencephalographic activation, apparently via inhibition of central cholinergic receptors.36 Monoamine oxidase inhibitors combined with meperidine, but not other opioids, produce a potentially lethal hyperthermia syndrome. Gamma-aminobutyric acid (GABA)-mimetic drugs reduce the antinociceptive effect of meperidine, but enhance the potency of fentanyl.37 Finally, meperidine has local anesthetic properties not shared by other opioids.38

Because meperidine is a “dirty” drug with numerous nonopioid actions, and thus numerous side effects, it is now considered a suboptimal analgesic. Nonetheless, the special antishivering action of meperidine makes it an obvious choice for facilitating induction of therapeutic hypothermia. A limitation of meperidine, though, is that the drug is, in part, metabolized to normeperidine. Normeperidine is neurotoxic and can cause seizures. It is thus prudent to restrict high-dose meperidine administration to a relatively short time such as 24 hours or less—especially in patients with renal insufficiency.

Nonopioids

Dozens of drugs have been evaluated as potential treatments for shivering, including meperidine, clonidine, nefopam, doxapram, ketanserin, physostigmine, tramadol, ondansetron, magnesium, dantrolene, and doxapram.27,40 Effective antishivering drugs, aside from muscle relaxants, presumably reduce the shivering threshold to below the actual core temperature. However, many drugs which are effective for postoperative shivering are insufficient for inducing therapeutic hypothermia. Magnesium, which decreases the shivering threshold imperceptibly,39 reportedly facilitates induction of hypothermia in volunteers who were also given meperidine.40

Clonidine (a central α-2 receptor agonist) is among the most effective treatments for perioperative shivering and remains “first-line” treatment of postoperative shivering in Europe. However, even substantial doses only slightly increase the threshold for sweating41 and only slightly reduce the vasoconstriction and shivering thresholds.34 The related drug, dexmedetomidine, produces somewhat more thermoregulatory inhibition35; however, the amount of inhibition would be insufficient to markedly facilitate induction of therapeutic hypothermia as a single agent.

Tramadol (which has opioid properties, but primarily inhibits norepinephrine neuronal reuptake), similarly, only slightly reduces the vasoconstriction and shivering thresholds.52 Nefopam, a benzoxazocine compound that is structurally related to orphenadrine and diphenhydramine,63 is intriguing. It is neither an opiate nor a nonsteroidal noninflammatory drug and has both spinal and supraspinal actions. It does not induce respiratory depression. Nefopam differs from other tested drugs in reducing the shivering threshold without altering the vasoconstriction or sweating thresholds. Thus, aside from muscle relaxants, it is the only drug that inhibits shivering without apparently otherwise impairing thermoregulation.44 The reduction was only about 1°C at a plasma concentration of 55 ng/mL, but is nonetheless encouraging because this is a relatively small concentration of the drug and the drug appears to have few side effects. Unfortunately, though nefopam is available in some European countries, it is not approved by the Food and Drug Administration in the United States.

Drug Combinations

No single drug appears sufficient to induce therapeutic hypothermia to 33 to 34°C in most patients. Combinations of drugs thus offer an alternative and have the further advantage of distributing side effects while simultaneously potentiating the therapeutic effect—impairment of thermoregulatory defenses. Two drugs can interact additively, which is the most common interaction; but they can also be antagonistic or synergistic. Synergistic combinations are obviously most attractive.
Several drug combinations have been formally evaluated for their ability to reduce the shivering threshold. For example, meperidine alone (at a plasma concentration of 0.3 μg/mL) reduces the shivering threshold 1.1°C, and dexmedetomidine (at a plasma concentration of 0.3 ng/mL) reduces the shivering threshold 0.7°C. The combination decreases the shivering threshold by 1.9°C, which indicates that the interaction was strictly additive; the normal shivering threshold is about 35.5°C; a 2°C reduction thus corresponds to a threshold of 34.5°C with the combination of dexmedetomidine and meperidine. Adapted from Doufas et al.45

Combining meperidine and dexmedetomidine thus produces exactly the expected reduction in the shivering threshold. Dexmedetomidine and buspirone also additively reduce the shivering threshold by about the same amount. Even an additive interaction is clinically useful because the major toxicities of the 2 drugs (respiratory depression and hypotension) are unlikely to be additive. In other words, adding dexmedetomidine to meperidine increases thermoregulatory inhibition without much increasing the incidence and severity of drug-related side effects.

But far more useful than an additive combination would be a synergistic interaction in which 2 drugs produce a greater-than-expected reduction in the shivering threshold. The only known combination of drugs that synergistically impairs shivering is that of meperidine and buspirone (a serotonin-1A partial agonist), and meperidine (at a plasma concentration of 0.6 μg/mL) reduces the shivering threshold by 2.3°C. Buspirone (60 mg orally) reduces the shivering threshold by 0.7°C. However, when a half dose of each drug is combined, the shivering threshold is reduced 2.3°C, which is significantly more than the expected 1.5°C decrease (Figure 7).46 A limitation of buspirone is that the drug is only available orally and requires about 1 hour after ingestion to reach peak plasma concentrations. The combination of buspirone and meperidine has nonetheless proven clinically useful and was the antishivering regimen used in a large multi-center study of therapeutic hypothermia for treatment of acute myocardial infarction. Short of general anesthesia, this combination is the best treatment for shivering currently available. For additional detail about therapeutic hypothermia, see Mayer and Sessler.9

**Physical Methods of Blunting Thermoregulatory Defenses**

Skin temperature contributes about 20% to autonomic control of shivering, with the remainder being derived from core temperature.17 An obvious consequence of this relationship is that surface cooling—which disproportionately cools the skin-surface—provokes a greater thermoregulatory defense than a comparable amount of hypothermia induced directly by core cooling, as with intravascular heat exchangers.47

The contribution of skin temperature to thermoregulatory control suggests that autonomic responses to direct core cooling can be moderated by simultaneous cutaneous warming. For example, a 4°C increase in mean-skin temperature compensates for 1°C of core hypothermia.48 The efficacy of this approach has been demonstrated, for example, by Sweney et al who reported that focal hand warming suppresses shivering in mildly hypothermic volunteers.49 The same group also reported that shivering can be suppressed by warming of the lower face combined with inhalation of heated and humidified air.50 Others have also reported that facial warming reduces shivering,51 as does radiant heating of the face and upper chest.52 The difficulty, though, is that the face and arms are only a small portion of the total skin surface. As might be expected, isolated hand or face warming
only trivially reduces the shivering threshold.\textsuperscript{45} In contrast, warming much of the skin surface is effective.\textsuperscript{53}

A further difficulty is that treatments reducing the shivering threshold only a couple tenths of a degree centigrade\textsuperscript{44} may be effective in volunteers or postoperative patients,\textsuperscript{54} but completely inadequate for the induction of therapeutic hypothermia. And, of course, warming systems that can maintain high skin temperatures eventually transfer considerable heat to the core. Nonetheless, this strategy has been used with considerable success in clinical trials that used endovascular cooling,\textsuperscript{56} but always combined with simultaneous pharmacological intervention.

### A Strategic Approach

Induction of therapeutic hypothermia in unconscious patients rarely provokes troublesome thermoregulatory responses. Typically, their thermoregulatory defenses are already blunted by coma. And if shivering nonetheless becomes problematic, unconscious patients can be given sedatives or even muscle relaxants since they are inevitably intubated, and usually mechanically ventilated.

The clinical difficulty is inducing therapeutic hypothermia in conscious patients, such as those with a typical stroke. These patients maintain active thermoregulatory defenses,\textsuperscript{41} which need to be blunted if hemodynamic instability\textsuperscript{20} and excessive autonomic activation\textsuperscript{21} are to be avoided. The best pharmacological approach appears to be a combination of drugs that induces sufficient thermal tolerance without excessive toxicity. The most-used combination is buspirone and meperidine.\textsuperscript{46} Other combinations that appear useful include dexametomidine combined with either meperidine\textsuperscript{45} or buspirone.

CUTANEOUS COOLING CONTRIBUTES 20\% TO CONTROL OF AUTONOMIC DEFENCES (Vasoconstriction and Shivering)\textsuperscript{17} AND 50\% TO BEHAVIOURAL RESPONSES (THERMAL DISCOMFORT).\textsuperscript{18} Surface cooling thus provokes considerably more aggressive defenses than comparable degrees of isolated core cooling. Direct core cooling, such as provided by infusion of cold fluid\textsuperscript{12} or endovascular heat exchangers,\textsuperscript{47} is therefore preferable—at least from a thermoregulatory perspective. Of course the trade-off is that endovascular systems, while cooling the core more quickly than surface methods, are invasive and relatively expensive. But to the extent that direct core cooling can be used, an optimal thermoregulatory approach is combine isolated core cooling with surface warming,\textsuperscript{53} while simultaneously giving drugs that synergistically induce thermal tolerance.

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