Anesthesiology
2000; 93:629–37


# *Core Cooling by Central Venous Infusion of Ice-cold (4°C and 20°C) Fluid*

## *Isolation of Core and Peripheral Thermal Compartments*

*Angela Rajek, M.D.,* Robert Greif, M.D.,† Daniel I. Sessler, M.D.,‡ James Baumgardner, M.D, Ph.D.,§ Sonja Laciny, M.D.,‖ Hiva Bastanmehr, B.S.#*



***Background:*** **Central venous infusion of cold fluid may be a useful method of inducing therapeutic hypothermia. The aim of this study was to quantify systemic heat balance and regional distribution of body heat during and after central infusion of cold fluid.**

***Methods:*** **The authors studied nine volunteers, each on two separate days. Anesthesia was maintained with use of isoflurane, and on each day 40 ml/kg saline was infused centrally over 30 min. On one day, the fluid was 20°C and on the other it was 4°C. By use of a tympanic membrane probe core (trunk and head) temperature and heat content were evaluated. Peripheral compartment (arm and leg) temperature and heat content were estimated with use of fourth-order regressions and integration over volume from 18 intramuscular thermocouples, nine skin temperatures, and "deep" hand and foot temperature. Oxygen consumption and cutaneous heat flux estimated systemic heat balance.**

***Results:*** **After 30-min infusion of 4°C or 20°C fluid, core temperature decreased 2.5 ± 0.4°C and 1.4 ± 0.2°C, respectively. This reduction in core temperature was 0.8°C and 0.4°C more than would be expected if the change in body heat content were distributed in proportion to body mass. Reduced core temperature resulted from three factors: (1) 10–20% because cutaneous heat loss exceeded metabolic heat production; (2) 50–55% from the systemic effects of the cold fluid *per se*; and (3) approximately 30% because the reduction in core heat content remained partially constrained to core tissues. The postinfusion period was associated with a rapid and spontaneous recovery of core temperature. This increase in core temperature was not associated with a peripheral-to-core redistribution of body heat because core temperature remained warmer than peripheral tissues even at the end of the infusion. Instead, it resulted from constraint of metabolic heat to the core thermal compartment.**

***Conclusions:*** **Central venous infusion of cold fluid decreases core temperature more than would be expected were the reduction in body heat content proportionately distributed. It thus appears to be an effective method of rapidly inducing therapeutic hypothermia. When the infusion is complete, there is a spontaneous partial recovery in core temperature that facilitates rewarming to normothermia. (Key words: Anesthesia; heat; hypothermia; temperature; thermoregulation.)**

MILD hypothermia for cerebral protection during neurosurgical procedures has received increasing attention

* Research Fellow, Department of Anesthesia and Perioperative Care, University of California–San Francisco; Attending Anesthesiologist, Department of Cardiothoracic and Vascular Anesthesia and Intensive Care Medicine, University of Vienna.

† Research Fellow, Department of Anesthesia and Perioperative Care, University of California–San Francisco; Attending Anesthesiologist, Department of Anesthesiology and Intensive Care Medicine, Donauspital.

‡ Assistant Vice President for Health Affairs, Associate Dean for Research, and Director, Outcomes Research™ Institute; Sam and Lolita Weakley Professor of Anesthesia, University of Louisville; Professor and Vice Chair, Ludwig Boltzmann Insitute.

§ Clinical Associate, Department of Anesthesia, University of Pennsylvania; Senior Scientist, SpectruMedix Corporation, State College, Pennsylvania.

‖ Research Fellow, Department of Anesthesia and Perioperative Care, University of California–San Francisco.

# Staff Research Associate, Department of Anesthesia and Perioperative Care, University of California–San Francisco. Received from the Outcomes Research™ Group, Department of Anesthesia and Perioperative Care, University of California–San Francisco, San Francisco, California; Department of Cardiothoracic and Vascular Anesthesia, University of Vienna, Vienna, Austria; Department of Anesthesiology and Intensive Care Medicine, Donauspital, Vienna, Austria; Outcomes Research™ Institute and Department of Anesthesia, University of Louisville, Louisville, Kentucky; Ludwig Boltzmann Institute for Clinical Anesthesia and Intensive Care, Vienna, Austria; Department of Anesthesia and General Intensive Care, University of Vienna, Vienna, Austria; and the Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania. Submitted for publication November 24, 1999. Accepted for publication March 21, 2000. Supported by grant No. GM58273 from the National Institutes of Health, Bethesda, Maryland; the Joseph Drown Foundation, Los Angeles, California; the Fonds zur Förderung der wissenschaftlichen Forschung and ThermaMed GmbH, Hamm, Germany.

Address correspondence to Dr. Sessler: University of Louisville, Abel Administration Center, Room 217, 323 East Chestnut Street, Louisville, Kentucky 40202-3866. Address electronic mail to: sessler@louisville.edu; on the World Wide Web: www.or.org

in recent years. There is a large amount of experimental evidence from animal studies indicating that mild hypothermia (33–35°C) provides substantial cerebral protection.[1–4] These studies also suggest that cerebral protection is increased further as brain temperature is decreased to 31°C.[2] Mild hypothermia may thus provide cerebral protection during the temporary focal ischemia that occurs during cardiac surgery and neurosurgical procedures, including cerebral aneurysm clipping.[5]

Rapidly reducing core temperature to less than 34°C without cardiopulmonary bypass has proven to be difficult. The initial 1–1.5°C decrease in core temperature after induction of general anesthesia results from core-to-peripheral redistribution of body heat.[6] Systemic heat loss then continues to decrease core temperature until patients are sufficiently hypothermic to trigger protective thermoregulatory vasoconstriction. However, this vasoconstriction is effective and usually results in a core-temperature plateau.[7]

Induction of core hypothermia using surface cooling is a relatively slow process, especially when patients are vasoconstricted.[8] A second difficulty with surface cooling is that mean skin temperature must be reduced considerably before core temperature decreases much. Because heat only flows down a temperature gradient, peripheral tissue temperatures well below 32°C are required before core temperature can even approach that value. This, of course, limits the rate at which core temperature can be therapeutically reduced. More importantly, peripheral tissue hypothermia makes rewarming extremely difficult once the critical surgical repair is complete. This is both because the resulting large core-to-peripheral tissue temperature gradient will promote an afterdrop and because core rewarming will be delayed while peripheral tissue heat content is repleted.

A recent study suggested that intravenous infusion of ice-cold fluid reduces core temperature far more than expected, apparently because the reduction in core heat content remains constrained to core tissues for some time.[9] Our aim was therefore to quantify systemic heat balance and regional distribution of body heat during infusion of cold fluid to determine the extent to which transient isolation of the core and peripheral thermal compartments facilitates core cooling and subsequent rewarming.

## Methods

With approval from the Committee on Human Research at the University of San Francisco, California, and written informed consent, we studied nine healthy young male volunteers. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, Raynaud syndrome, sickle-cell disease, cryoglobulinemia, or malignant hyperthermia.

### *Protocol*

Studies started at approximately 8:30 AM, and volunteers fasted during the preceding 8 h. Throughout the study, minimally clothed volunteers reclined on an operating table set in chaise-lounge position. An intravenous cannula was inserted in the left antecubital vein. Each volunteer participated on 2 study days, separated by at least 48 h.

Anesthesia was induced by intravenous administration of propofol (4 mg/kg) and vecuronium bromide (0.1 mg/kg). The volunteers' tracheas were intubated and mechanical ventilation was adjusted to maintain end-tidal carbon dioxide pressure near 35 mmHg. Anesthesia was maintained with isoflurane at 0.6 minimum alveolar concentration in 30% oxygen and air throughout the study period. Fresh gas flow was maintained at 6 l/min. An infusion of vecuronium was adjusted to maintain one mechanical twitch in response to supramaximal train-of-four electrical stimulation of the ulnar nerve at the wrist. An 18-gauge central venous catheter then was inserted into the superior vena cava.

During the first 1.5 h after induction of anesthesia, core temperature was allowed to decrease *via* core-to-peripheral redistribution and passive systemic heat loss. On each study day, we infused 40 ml/kg saline 0.9% through the central venous catheter over a 30-min period. The fluid was given *via* an infusion pump. We have used similar infusions in previous studies but without quantifying heat balance and distribution.[10–13] Fluid temperature was randomly assigned to either 4°C or 20°C on the first study day, and each volunteer was assigned to receive the alternative temperature on the second study day. Ninety minutes later, the neuromuscular block was antagonized by giving the volunteers atropine 0.5 mg and edrophonium 50 mg, and anesthesia was discontinued. The volunteers subsequently participated in a rewarming study (unpublished data).

### *Measurements*

End-tidal isoflurane and carbon dioxide concentrations were monitored using a Capnomac Ultima (Datex Medical Instruments, Tewksbury, MA). Blood pressures, arterial saturation, and heart rates were measured using monitors incorporated into an Ohmeda Modulus CD anesthesia machine (Ohmeda, Inc., Salt Lake City, UT).

Temperature of the administered intravenous fluid was measured with a needle thermocouple inserted into the fluid stream adjacent to the catheter insertion site. Arteriovenous shunt vasoconstriction was evaluated with forearm minus fingertip, skin-temperature gradients.[14] Gradients exceeding 0°C were considered evidence of vasoconstriction because that value is associated with onset of the core-temperature plateau during general anesthesia.[7]

Energy expenditure, derived from oxygen consumption and carbon dioxide production, were measured using a metabolic monitor (Deltatrac, SensorMedics Corp., Yorba Linda, CA). Measurements were averaged over 5-min intervals and recorded every 5 min. Area-weighted heat flux and temperatures from 15 skin-surface sites were measured using thermal flux transducers (Concept Engineering, Old Saybrook, CT). As in previous studies,[6,15] measured cutaneous heat loss was augmented by 10% to account for insensible transcutaneous evaporative loss and reduced 3% to compensate for the skin covered by the volunteers' shorts. We further augmented cutaneous loss by 10% of the metabolic rate (as determined from oxygen consumption) to account for respiratory loss. We defined flux as positive when heat traversed skin to the environment.

Arm and leg tissue temperatures were determined as previously described.[6,16] Briefly, the length of the thigh (groin to midpatella) and lower leg (midpatella to ankle) were measured in centimeters. Circumference was measured at the mid–upper thigh, mid–lower thigh, mid–upper calf, and mid–lower calf. At each circumference, right leg muscle temperatures were recorded using 8-, 18-, and 38-mm, 21-gauge needle thermocouples (Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO) inserted perpendicular to the skin surface. Skin-surface temperatures were recorded immediately adjacent to each set of needles and directly posterior to each set. Subcutaneous temperature was measured on the ball of the foot using a Coretemp (Terumo Medical Corp., Tokyo, Japan) "deep tissue" thermometer.[17,18] This device estimates tissue temperature approximately 1 cm below the skin surface.

The lengths of the right arm (axilla to elbow) and forearm (elbow to wrist) were measured in centimeters. The circumference was measured at the midpoint of each segment. As in the right leg, 8-, 18-, and 38-mm needle thermocouples were inserted into each segment. Skin-surface temperatures were recorded immediately adjacent to each set of needles. Core, skin-surface, and muscle temperatures were recorded from thermocouples connected to two calibrated Iso-Thermex 16-channel electronic thermometers (Columbus Instruments International, Corp., Columbus, OH) and Mon-a-Therm 6510 two-channel thermometers (Mallinckrodt Anesthesiology Products). Temperatures and thermal fluxes were measured at 1-s intervals, then averaged and recorded every 5 min.

*Data Analysis*

The leg was divided into five segments: upper thigh, lower thigh, upper calf, lower calf, and foot. Each thigh and calf segment was further divided into an anterior and posterior section, with one third of the estimated mass considered to be posterior.

Anterior segment tissue temperatures, as a function of radial distance from the center of the leg segment, were calculated using skin-surface and muscle temperatures and using fourth-order regressions. Temperature at the center of the thigh was set to core temperature. In contrast, temperature at the center of the lower leg segments was estimated from the regression equation with no similarity assumption. Anterior limb heat content was estimated from these temperatures, as previously described,[6] using the formula:

$$Q_{(0 \rightarrow r)} = 2(\Pi r^2 L)\rho s[a_0 + (a_2 r^2/2) + (a_4 r^4/3)] \quad (1)$$

where $Q_{(0 \rightarrow r)}$ (cal) is heat content of the leg segment from the center to radius r, L (cm) is the length of the leg segment (*i.e.*, groin to midthigh, midcalf to ankle), $\rho$ (g/cm$^3$) is tissue density, s (cal · °C$^{-1}$ · g$^{-1}$) is the specific heat of leg tissues, $a_0$ (°C) is the temperature at the center of the leg segment, and $a_2$ (°C/cm$^2$) and $a_4$ (°C/cm$^4$) are the fourth-order regression constants. The specific heat of muscle was taken as 0.89 cal · °C$^{-1}$ · g$^{-1}$ and density as 1.06 g/cm$^3$.[19]

Rather than assume full radial symmetry, we assumed only that radial temperature distribution in the posterior leg segments would also be parabolic. Accordingly, we calculated the regression constant $a_2$ in the posterior leg segments from $a_0$ determined from the adjacent anterior segment and the posterior segment skin temperature. Posterior segment tissue heat contents were then determined from equation 1. Average segment tissue temperatures were determined by the equation

$$T_{Ave} = a_0 + (a_2 r^2/2) \quad (2)$$

We have previously described the derivation of these equations and their limitations.[16]

Deep temperature, measured on the ball of the foot, was assumed to represent the entire foot. Foot heat content thus was calculated by multiplying foot temperature by the mass of the foot and the specific heat of muscle. Average temperatures of the thigh and lower leg (calf and foot) were calculated by weighting values from each of the nine segments in proportion to their estimated masses. The right and left leg were treated comparably throughout this study, so we assumed that average tissue temperatures in the two limbs were similar.

Arm tissue temperature and heat content was calculated from the parabolic version of equation 1. In the arms, we assumed full radial symmetry and thus did not separately calculate posterior segment values. Palm deep temperature was assumed to represent that of the entire hand. Hand heat content thus was calculated by multiplying deep palm temperature by the mass of the hand and the specific heat of muscle. As in the leg, average temperatures of the arm and forearm (forearm and hand) were calculated by weighting values from each of the three segments in proportion to their estimated masses.

Changes in trunk and head heat content were modeled simply by multiplying the weight of the trunk and head by the change in core temperature and the average specific heat of human tissues. Trunk and head weight was estimated by subtracting the calculated weight of the extremities (from the radial integration) from the total weight of each subject. Mean body temperature was calculated from the weighted average of peripheral tissue and core temperatures. Excess core heat was determined by subtracting the actual change (change in tympanic membrane temperature multiplied by the specific heat of human tissue and the weight of the trunk and head) from the expected change in that region (systemic heat balance multiplied by the fractional weight of the trunk and head). Excess core heat thus identifies the extent to which changes in body heat content are disproportionately distributed between the core and peripheral thermal compartments. Excess core temperature was determined by subtracting core temperature from mean body temperature.

As in previous investigations, changes in whole-body heat content on each study day were calculated using two independent methods: (1) time integral of metabolic heat production minus cutaneous heat loss, combined with cooling effect of the fluid; and (2) sum of extremity and core tissue heat contents.

Results are expressed as mean ± SD. Differences in tissue temperatures and heat content were considered statistically significant at $P < 0.01$.

## Results

The volunteers' average height was 175 ± 5 cm (mean ± SD), weight was 72 ± 11 kg, and age was 27 ± 3 yr. Estimated mass of the legs (including the feet) was 26 ± 5 kg; the legs thus represented approximately 36% of the volunteers' total mass. Similarly, estimated mass of the arms (including the hands) was 9 ± 2 kg, thus representing approximately 12% of the volunteers' body mass. Ambient temperature during the study period was 21.4 ± 0.5°C.

After 1.5 h of anesthesia, core temperature decreased to 35.7°C on each study day. All volunteers were vasoconstricted before the central venous infusion started. Forearm minus fingertip gradient was 2.4 ± 2.7°C before the start of the 4°C infusion and was 3.2 ± 3.1°C before the start of 20°C infusion. The infusion rate on both days was 96 ± 13 ml/min over 30 min, and the infused volume was 2.9 ± 0.2 l of saline.

Infusion of 4°C (4.1 ± 0.1°C) and 20°C (20.2 ± 0.1°C) fluid over 30 min decreased core temperature by 2.5 ± 0.4°C and 1.4 ± 0.2°C, respectively. As mean body temperature decreased by 1.8 ± 0.1°C and 1.0 ± 0.1°C, respectively, the decrease in core temperature was greater than expected. Peripheral tissue temperature after infusion of fluid at 4°C and 20°C decreased considerably less than either core or mean body temperatures (1.3 ± 0.2°C *vs.* 0.8 ± 0.2°C; fig. 1).

Core and peripheral heat content did not differ before start of infusion on the study days. Core heat content after 4°C and 20°C infusion decreased by 78 ± 17 kcal and 43 ± 9 kcal. Peripheral heat content decreased 39 ± 14 kcal and 25 ± 5 kcal, respectively (fig. 2).

Central venous infusion of 40 ml/kg of fluid reduced metabolic rate 5 kcal/h on the 20°C day and 11 kcal/h on the 4°C day. Cutaneous heat loss on both days exceeded metabolic heat production throughout the study period and was slightly higher after 20°C fluid infusion. This decrease in body heat content, if distributed in proportion to tissue mass, would correspond to a 0.3 ± 0.1°C reduction in core temperature; this represents 10% and 20% of the observed total decrease during 4°C and 20°C fluid infusions.

Infusion of 40 ml/kg 4°C and 20°C fluid decreased body heat content at a rate of 183 ± 28 kcal/h and 90 ± 14 kcal/h throughout the 30-min infusion period (fig. 3). Fluid-induced reduction in body heat content, if proportionately distributed, would account for 1.4°C and 0.7°C of the core cooling. This represents 55% of the total decrease during the 4°C infusion and 50% during the 20°C infusion.

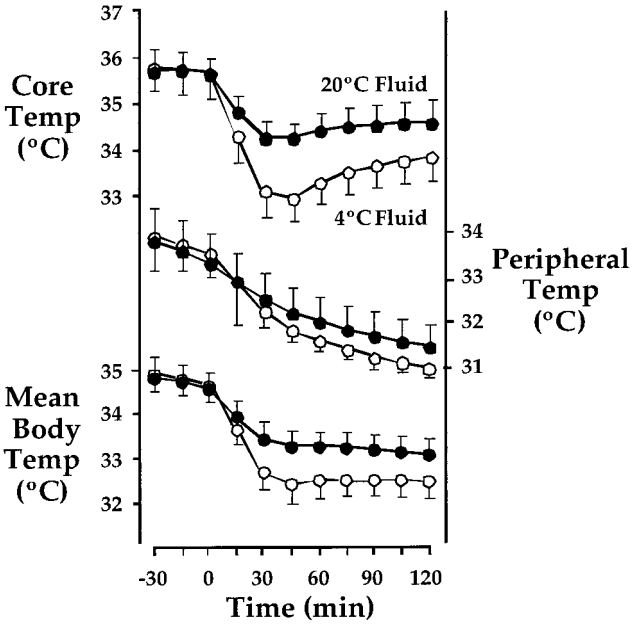


**Fig. 1. Core, peripheral tissue, and mean body temperatures before and after fluid infusion. The infusion of 40 ml/kg at 4°C (open circles) and 20°C (filled circles) began at elapsed time zero and lasted for 30 min. Results are presented as mean ± SD.**

The core-to-peripheral temperature gradient before 4°C and 20°C fluid infusion was similar: 2.1 ± 1.1°C and 2.3 ± 0.8°C, respectively. The gradient decreased after fluid infusion and was lower after ice-cold fluid infusion. The core-to-peripheral temperature gradient decreased to 0.9 ± 0.9°C during the 4°C fluid infusion to 2.8 ± 0.8°C, whereas it decreased only to 1.7 ± 0.6°C during fluid infusion. During the 90 min after completion of the

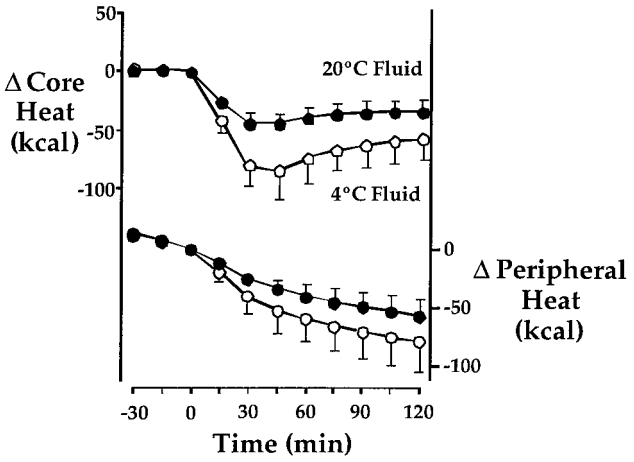


**Fig. 2. Change in core and peripheral heat contents before and after fluid infusion. The infusion of 40 ml/kg at 4°C (open circles) and 20°C (filled circles) began at elapsed time zero and lasted for 30 min. Results are presented as mean ± SD.**

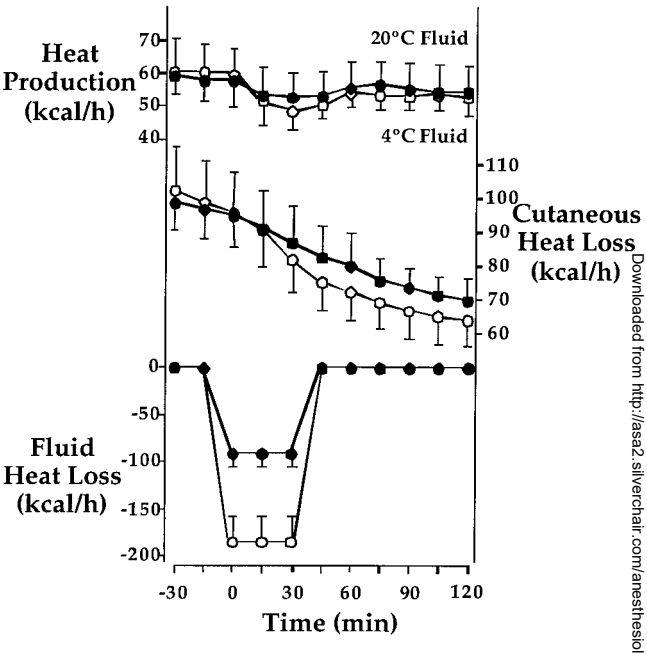


**Fig. 3. Heat production, cutaneous heat loss, and heat loss by fluid before and after fluid infusion. The infusion of 40 ml/kg at 4°C (open circles) and 20°C (filled circles) began at elapsed time zero and lasted for 30 min. Results are presented as mean ± SD.**

infusion, the core-to-peripheral temperature gradient increased to 2.8 ± 0.8°C when the volunteers were given 4°C fluid and to 3.1 ± 0.8°C after 20°C fluid infusion.

With 4°C and 20°C fluid infusion, core temperature decreased by 0.8 ± 0.1°C and 0.4 ± 0.3°C more than expected if the total change in body heat content had been proportionately distributed across the core and peripheral thermal compartments. Heat content of the core compartment at the end of 4°C and 20°C fluid infusion was 24 ± 13 kcal and 12 ± 9 kcal less than expected, respectively. This represents 30% of the total decrease observed during the 4°C and 20°C infusion (fig. 4, table 1).

Total body heat content derived independently from tissue temperatures (extremities and core) after 4°C and 20°C fluid infusion was 8 kcal and 5 kcal higher than overall systemic heat content derived from heat loss and heat production. This difference was compensated by a greater decrease in overall heat content during the 90 min after cooling. Thus, changes in body heat content and overall heat content at the end of the study period were almost identical whether determined from core and peripheral tissue temperatures or from overall heat content as determined from systemic heat balance (fig. 5).

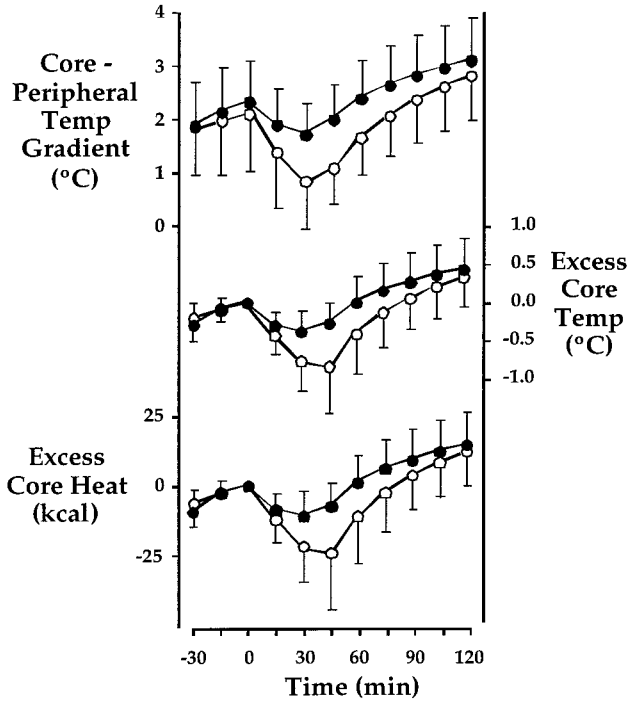


**Fig. 4. Core-to-peripheral temperature gradient, excess core temperature, and excess core heat before and after fluid infusion. The infusion of 40 ml/kg at 4°C (open circles) and 20°C (filled circles) began at elapsed time zero and lasted 30 min. Results are presented as mean ± SD.**

## Discussion

Central venous infusion of fluid was effective, reducing core temperature 2.5 ± 0.4°C during infusion of 4°C fluid and 1.4 ± 0.2°C during infusion of 20°C fluid. Three factors contributed to this observed decrease in core temperature.

The first factor contributing to core hypothermia during the fluid infusion was simply the imbalance between metabolic heat production and cutaneous heat loss. Central venous infusion of 40 ml/kg of fluid reduced metabolic rate 5 kcal/h on the 20°C day and 11 kcal/h on the 4°C day. This is consistent with previous reports that reductions in body temperature decrease metabolic rate only approximately 7%/°C.[20–22] Interestingly, metabolic rate subsequently increased along with core temperature, although mean body temperature remained nearly constant after the infusions were complete. Metabolic heat production thus appears to depend more on core than peripheral tissue temperature, which is consistent with the fact that the most metabolically active organs are centrally located.

In contrast, cutaneous heat loss decreased approximately 8% during infusion of 20°C fluid and approximately 15% during infusion of 4°C fluid. However, cutaneous heat loss always exceeded metabolic heat production as might be expected in a 21.5°C environment. Body heat content thus decreased approximately 18 kcal throughout the infusion period, even without considering the effects of cold fluid. Assuming this imbalance was proportionately distributed across body tissues, only 0.3 ± 0.1°C of the core cooling can be attributed to excessive cutaneous heat loss. This represents just 10% of the observed total decrease during the 4°C infusion, and just 20% during the 20°C infusion.

For the purpose of this analysis, we assumed that the imbalance in systemic heat content was proportionately distributed between the core and peripheral compartments. This is not actually the case because the reduction in metabolic heat production most directly decreases core heat content and therefore core temperature. Similarly, the

**Table 1. Tissue Temperature, Heat Content, and Core-to-peripheral Temperature Gradient**

| | 20°C Fluid | 4°C Fluid |
|---|---|---|
| Before cooling | | |
| Core temperature (°C) | 35.7 ± 0.3 | 35.7 ± 0.5 |
| Peripheral tissue temp (°C) | 33.3 ± 0.7 | 33.5 ± 0.7 |
| Core-to-peripheral temperature gradient (°C) | 2.3 ± 0.8 | 2.1 ± 1.2 |
| Mean body temp (°C) | 34.6 ± 0.4 | 34.7 ± 0.5 |
| End of 30-minute cooling period | | |
| Core temperature (°C) | 34.3 ± 0.4 | 33.1 ± 0.6 |
| Peripheral tissue temp (°C) | 32.5 ± 0.6 | 32.3 ± 0.6 |
| Core-to-peripheral temperature gradient (°C) | 1.7 ± 0.6 | 0.9 ± 0.9 |
| Mean body temp (°C) | 33.4 ± 0.4 | 32.7 ± 0.4 |
| Decrease in core heat content (kcal) | 43 ± 9 | 78 ± 17 |
| Decrease in peripheral heat content (kcal) | 25 ± 5 | 39 ± 14 |
| Decrease in total body heat content (kcal) | 68 ± 11 | 117 ± 27 |
| Excess core cooling (kcal) | 12 ± 9 | 24 ± 13 |
| End of 90-minute observation period | | |
| Core temperature (°C) | 34.6 ± 0.5 | 33.9 ± 0.5 |
| Peripheral tissue temp (°C) | 31.5 ± 0.5 | 31.0 ± 0.4 |
| Core-to-peripheral temperature gradient (°C) | 3.1 ± 0.8 | 2.8 ± 0.8 |
| Mean body temp (°C) | 33.1 ± 0.4 | 32.5 ± 0.4 |
| Decrease in core heat content (kcal) | 34 ± 11 | 56 ± 17 |
| Decrease in peripheral heat content (kcal) | 57 ± 16 | 79 ± 25 |
| Decrease in total body heat content (kcal) | 91 ± 17 | 135 ± 39 |

Data presented as mean ± SD.

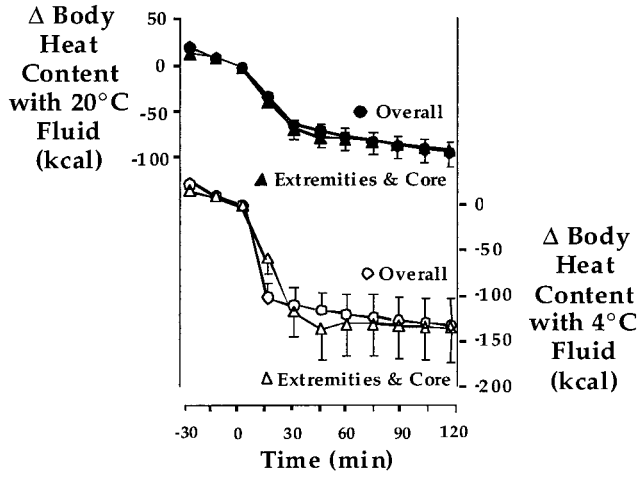


**Fig. 5. Change in body heat content, as determined by core and peripheral tissue temperatures (extremities and core) and systemic heat balance (overall). Results are presented as mean ± SD.**

reduction in cutaneous heat loss most directly moderates further cooling of peripheral tissues. These factors oppose each other, with the result that infusion of cold fluid reduces core temperature more than would be expected (*via* reduction in metabolic rate) and reduces peripheral tissue temperature less than would be expected (*via* reduction in cutaneous heat loss).

The second factor contributing to core hypothermia was that infusion of 4°C and 20°C fluid *per se* decreased body heat content 87 kcal and 42 kcal, respectively. Again assuming this cooling was proportionately distributed throughout the body, we can attribute 1.4°C and 0.7°C of the core cooling to a fluid-induced reduction in body heat content. This represents 55% of the total during the 4°C infusion and 50% during the 20°C infusion. Roughly half of the observed core hypothermia thus results directly from the cooling effect of the infused fluid.

The third factor contributing to core cooling during cold fluid infusion was relative isolation of the core and peripheral thermal compartments. With each fluid temperature, the reduction in core temperature and heat content far exceeded the reductions in peripheral tissue. Consequently, core temperature also decreased considerably more than mean body temperature. This can be expressed as excess core cooling (compared with the amount that would be expected were the total change in body heat content proportionately distributed). Our data indicate that the core was 24 ± 13 kcal and 12 ± 9 kcal cooler than might otherwise be expected at the end of the 30-min infusion period. Constraint of the fluid-induced cooling to the core thermal compartment thus contributed 0.8°C and 0.4°C to the reduction in core temperature observed during infusion of 4°C and 20°C fluid. This represents 30% of the total observed during both the 4°C and the 20°C infusion.

Constraint of fluid-induced cooling to the core thermal compartment contributed significantly to core hypothermia, *i.e.*, the core cooled approximately 30% more than would be expected were the change in systemic heat balance proportionately distributed among body tissues. Although this contribution was somewhat less than estimated in a clinical investigation,[9] our data confirm the previous conclusion that isolation of core and peripheral thermal compartments makes central infusion of cold fluid more effective than might otherwise be expected.

Surface cooling has several disadvantages compared with cold fluid infusion. The most obvious is that surface cooling is relatively slow: surface cooling (except during water immersion) cannot decrease core temperature nearly as quickly as fluid administration.[10] An additional disadvantage is that surface cooling markedly reduces peripheral tissue temperature.[17] This has two unfortunate consequences. The first is that with surface cooling, mean body temperature and body heat content decrease out of proportion to the reduction in core temperature. During rewarming, it is thus necessary to transfer larger amounts of heat than might be expected based only on the reduction in core temperature. The second unfortunate consequence is that surface cooling markedly increases the core-to-peripheral temperature gradient. When cutaneous warming is then substituted for cooling, both conductive[23–25] and convective[24,26] factors contribute to a core-temperature afterdrop that must be overcome before any net increase in core temperature can occur.[20,27–29] Instead of an afterdrop, the period immediately after infusion of cold fluid was associated with a rapid and spontaneous recovery of core temperature. For example, after infusion of 4°C fluid decreased core temperature 2.5 ± 0.4°C, the temperature spontaneously increased 0.7°C in the subsequent hour. This increase was all the more remarkable when one considers that systemic heat balance was negative throughout this entire period. From a clinical perspective, spontaneous recovery of core temperature makes infusion-based cooling desirable because it facilitates return to normothermia and presumably minimizes unnecessary risk of hypothermic complications.[30–33]

The roughly exponential shape of the core-temperature recovery and previous mathematical modeling[9] suggested that core temperature increased after the infusion ended because of a "reverse afterdrop," *i.e.*, a peripheral-

to-core redistribution of heat. One of our major experimental purposes was to confirm this mechanism and quantify its magnitude.

Infusion of cold fluid decreased core temperature far more than peripheral tissue temperature. For example, infusion of fluid at 4°C decreased core temperature 2.5 ± 0.4°C but peripheral temperature only 1.3 ± 0.2°C. The core-to-peripheral tissue-temperature gradient thus decreased from 2.1 ± 1.1°C to 0.9 ± 0.9°C. This is a substantial and clinically important reduction, but the gradient nonetheless remained positive, *i.e.*, core temperature remained greater than peripheral tissue temperature even at the end of the 4°C infusion. Any net flow of heat from the cool periphery to a warmer core compartment would violate the Second Law of Thermodynamics—making it immediately apparent that another mechanism must be sought.

The solution to this apparent paradox lies in the plot of excess core heat (fig. 4). The importance of this curve is that it identifies the extent to which changes in body heat content are disproportionately distributed between the core and peripheral thermal compartments. Excess core heat therefore does not necessarily indicate that the core is warmer; instead, it means that the core is warmer than would be expected for a given body heat content if the changes were distributed between the compartments in proportion to their respective weights.

Excess core heat was negative by nearly 25 kcal at the end of the 4°C infusion, indicating that the core compartment was disproportionately cold. This is the approximate 30% constraint of fluid-induced cooling to the core thermal compartment discussed previously. During the subsequent approximate 45 min, excess core heat returned to zero. This is equivalent to saying that the changes in body heat content induced by fluid administration and continued negative net heat balance were again proportionately distributed between the core and peripheral thermal compartments after approximately 75 min elapsed. Subsequently, however, excess core heat continues to increase, indicating that the core was disproportionately warm at the end of the study.

The key to understanding the excessive core heat that was observed during the final 45 min of the study is the effect of thermoregulatory vasoconstriction. The volunteers were vasoconstricted throughout the infusion and the subsequent 90-min observation period. The significance of this is that we have previously demonstrated that arteriovenous shunt vasoconstriction effectively isolates the core and peripheral thermal compartments, allowing core heat content to increase even during periods of negative systemic heat balance.[7] That is exactly what happened during this study.

Mean body temperature and body heat content decreased slightly during the postinfusion period. However, metabolic heat (which is mostly generated in the core thermal compartment) remained largely restricted to the core. As a result, core temperature and excessive core heat increased while peripheral tissue temperature decreased. The postinfusion recovery in core temperature thus did not result from a peripheral-to-core redistribution of body heat, which would require an impossible flow of heat from cold to warm tissues. Instead, it resulted from thermoregulatory vasoconstriction, which constrained metabolic heat to the core thermal compartment—in effect, reestablishing the normal (*i.e.*, preanesthetic) core-to-peripheral tissue-temperature gradient.

We used a central venous catheter is this protocol, as we have previously.[12,13] However, fluid can be given through an anticubital catheter with similar benefit. We evaluated only a single fluid volume (40 ml/kg) at two temperatures. Obviously this volume cannot be safely given to all patients and would be inappropriate during some procedures. However, 20 ml/kg of fluid at 4°C could be given to most patients and would produce about the amount of core cooling observed with 40 ml/kg of fluid at 20°C. The effects of other fluid volumes and temperatures can presumably be estimated from the data presented here by determining the "cold load" from the volume, temperature, and specific heat of the infused fluid.

Many of our measurements are only approximations of values we would prefer to know with greater accuracy. Furthermore, we made numerous extrapolations and assumptions in our analysis. Most of these have previously been described in some detail.[6,16] As part of our study, we evaluated body heat content both from systemic heat balance (metabolic rate minus cutaneous heat loss) and measured changes in core and extremity tissue temperatures. The results were similar with these two independent methods, which suggests that neither was seriously in error.

In summary, the decrease in core temperature during central venous infusion of 4°C and 20°C fluid resulted from three factors: (1) 10–20% because cutaneous heat exceeded metabolic heat production; (2) 5–55% from the systemic effects of the cold fluid *per se*; and (3) 30% because the reduction in core heat content remained partially constrained to core tissues. Central venous infusion of cold fluid decreases core temperature more than would be expected were the reduction in body heat content proportionately distributed. It thus appears

to be an effective method of rapidly inducing therapeutic hypothermia. The postinfusion period was associated with a rapid and spontaneous recovery of core temperature that will facilitate rewarming to normothermia. Spontaneous rewarming resulted from constraint of metabolic heat to the core thermal compartment rather than a peripheral-to-core redistribution of body heat.

The authors thank Mallinckrodt Anesthesiology Products, Inc., St. Louis, Missouri, for donating the thermocouples.

## References

1. Baker KZ, Young WL, Stone GJ, Kader A, Baker CJ, Solomon RA: Deliberate mild intraopertive hypothermia for craniotomy. ANESTHESIOLOGY 1994; 81:361–7

2. Busto R, Dietrich WD, Globus MY-T, Valdés I, Scheinberg P, Ginsberg MD: Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cerebral Blood Flow Metab 1987; 7:729–38

3. Busto R, Dietrich WD, Globus MY-T, Ginsberg MD: Postischemic moderate hypothermia inhibits CA1 hippocampal ishemic neuronal injury. Neurosci Lett 1989; 101:299–304

4. Bickler PE, Buck LT, Hansen BM: Effects of isoflurane and hypothermia on glutamate receptor-mediated calcium influx in brain slices. ANESTHESIOLOGY 1994; 81:1461–9

5. Hindman BJ, Todd MM, Gelb AW, Loftus CM, Craen RA, Schubert A, Mahla ME, Torner JC: Mild hypothermia as a protective therapy during intracranial aneurysm surgery: A randomized prospective pilot trial. Neurosurgery 1999; 44:23–32

6. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C: Heat flow and distribution during induction of general anesthesia. ANESTHESIOLOGY 1995; 82:662–73

7. Kurz A, Sessler DI, Christensen R, Dechert M: Heat balance and distribution during the core-temperature plateau in anesthetized humans. ANESTHESIOLOGY 1995; 83:491–9

8. Kurz A, Sessler DI, Birnbauer F, Illievich U, Spiss C: Thermoregulatory vasoconstriction impairs active core cooling. ANESTHESIOLOGY 1995; 82:870–6

9. Baumgardner JE, Baranov D, Smith DS, Zager EL: The effectiveness of rapidly infused intravenous fluids for inducing moderate hypothermia in neurosurgical patients. Anesth Analg 1999; 89:163–9

10. Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. ANESTHESIOLOGY 1994; 80:780–8

11. Sessler DI, Moayeri A, Støen R, Glosten B, Hynson J, McGuire J: Thermoregulatory vasoconstriction decreases cutaneous heat loss. ANESTHESIOLOGY 1990; 73:656–60

12. Tayefeh F, Plattner O, Sessler DI, Ikeda T, Marder D: Circadian changes in the sweating-to-vasoconstriction interthreshold range. Pflügers Arch 1998; 435:402–6

13. Lenhardt R, Greif R, Sessler DI, Laciny S, Rajek A, Bastanmehr H: Relative contribution of skin and core temperatures to vasoconstriction and shivering thresholds during isoflurane anesthesia. ANESTHESIOLOGY 1999; 91:422–9

14. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. ANESTHESIOLOGY 1990; 73:541–5

15. Plattner O, Xiong J, Sessler DI, Christensen R, Turakhia M, Dechert M, Clough D: Rapid core-to-peripheral tissue heat transfer during cutaneous cooling. Anesth Analg 1996; 82:925–30

16. Belani K, Sessler DI, Sessler AM, Schroeder M, McGuire J, Washington D, Moayeri A: Leg heat content continues to decrease during the core temperature plateau in humans. ANESTHESIOLOGY 1993; 78:856–63

17. Togawa T, Nemoto T, Yamazaki T, Kobayashi T: A modified internal temperature measurement device. Med Biol Eng 1976; 14:361–4

18. Fox RH, Solman AJ: A new technique for monitoring the deep body temperature in man from the intact skin surface. J Physiol (US) 1970; 212:8–10

19. Burton AC: Human calorimetry: The average temperature of the tissues of the body. J Nutr 1935; 9:261–80

20. Hynson JM, Sessler DI, Moayeri A, McGuire J: Absence of nonshivering thermogenesis in anesthetized humans. ANESTHESIOLOGY 1993; 79:695–703

21. Plattner O, Semsroth M, Sessler DI, Papousek A, Klasen G, Wagner O: Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. ANESTHESIOLOGY 1997; 86:772–7

22. Orkin FK: Physiologic disturbances associated with induced hypothermia, Complications in Anesthesiology. Edited by Orkin FK, Cooperman LH. Philadelphia, Lippincott Company, 1983, pp 626–37

23. MacKenzie MA, Hermus ARMM, Wollersheim HCH, Binkhorst RA, Pieters GFFM: Thermoregulation and afterdrop during hypothermia in patients with poikilothermia. Q J Med 1993; 86:205–13

24. Romet TT: Mechanism of afterdrop after cold water immersion. J Appl Physiol 1988; 65:1535–8

25. Webb P: Afterdrop of body temperature during rewarming: An alternative explanation. J Appl Physiol 1986; 60:385–90

26. Giesbrecht GG, Bristow GK: A second postcooling afterdrop: More evidence for a convective mechanism. J Appl Physiol 1992; 73:1253–8

27. Plattner O, Kurz A, Sessler DI, Ikeda T, Christensen R, Marder D, Clough D: Efficacy of intraoperative cooling methods. ANESTHESIOLOGY 1997; 87:1089–95

28. Bristow GK, Biesbrecht GG, Sessler DI: Leg temperature and heat content in humans during immersion hypothermia and rewarming. Aviat Space Environ Med 1994; 65:220–6

29. Giesbrecht GG, Sessler DI, Mekjavic IB, Schroeder M, Bristow GW: Treatment of immersion hypothermia by direct body-to-body contact. J Appl Physiol 1994; 76:2373–9

30. Kurz A, Sessler DI, Lenhardt RA, Study of wound infections and temperature group: Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 1996; 334:1209–15

31. Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A: Mild intraoperative hypothermia increases blood loss and allogeneic transfusion requirements during total hip arthroplasty. Lancet 1996; 347:289–92

32. Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, Beattie C: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. JAMA 1997; 277:1127–34

33. Lenhardt R, Marker E, Goll V, Tschernich H, Kurz A, Sessler DI, Narzt E, Lackner F: Mild intraoperative hypothermia prolongs postoperative recovery. ANESTHESIOLOGY 1997; 87:1318–23