Nifedipine and Intraoperative Core Body Temperature in Humans

Nicolas Vassilieff, M.D.,* Nadia Rosencher, M.D.,* Daniel I. Sessler, M.D.,†
Christian Conseiller, M.D.,‡ André Lienhart, M.D.§

Background: Initial anesthetic-induced hypothermia results largely from core-to-peripheral redistribution of heat. Nifedipine administration may minimize hypothermia by inducing vasodilation well before induction of anesthesia. Although vasodilation would redistribute heat to peripheral tissues, thermoregulatory responses would maintain core temperature. After equilibration, the patient would be left vasodilated, with a small core-to-peripheral temperature gradient. Minimal redistribution hypothermia may accompany subsequent induction of anesthesia, because heat flow requires a temperature gradient. In contrast, similar vasodilation concurrent with anesthetic-induced vasodilation may augment redistribution hypothermia. Accordingly, the authors tested the hypothesis that nifedipine treatment for 12 h before surgery would minimize intraoperative redistribution hypothermia, whereas nifedipine treatment immediately before induction of anesthesia would aggravate hypothermia.

Methods: Patients undergoing hip arthroplasty were randomly assigned to: (1) 20 mg long-acting nifedipine orally 12 h before surgery, and 10 mg sublingually 1.5 h before surgery (n = 10); (2) nifedipine 10 mg sublingually just before induction of anesthesia (n = 10); and (3) no nifedipine (control, n = 10). Anesthesia was maintained with isoflurane and 60% nitrous oxide. Administered intravenous fluids were heated, but the patients were not otherwise actively warmed.

Results: Core temperature decreased 0.8° C in the first hour of surgery in the patients given nifedipine the night before and the morning of surgery, which was significantly less than in the control group (1.7° C in the first hour). In contrast, core temperature decreased 2.0° C in the first hour of surgery in the patients given nifedipine immediately before induction of anesthesia. During the subsequent 70–130 min of anesthesia, core temperature decreased at roughly comparable rates in each group. After 130 min of anesthesia, core temperature in the two nifedipine-treated groups differed by 1.6° C, and the temperatures in all three groups differed significantly.

Conclusions: Vasodilation induced by nifedipine well before induction of anesthesia minimized redistribution hypothermia, presumably by decreasing the core-to-peripheral tissue temperature gradient. In contrast, redistribution hypothermia was aggravated by administration of the same drug immediately before induction of anesthesia. Drug-induced modulation of vascular tone thus produces clinically important alterations in intraoperative core temperature. (Key words: Brain: hypothalamus. Calcium-channel blockers: nifedipine. Hypothermia. Temperature, regulation: setpoint; threshold; vasoconstriction. Thermoregulation. Vasodilator.)

* Attending Anesthesiologist, Department of Anesthesiology and Intensive Care, Cochin Port-Royal University Hospital.

† Associate Professor of Anesthesia, Department of Anesthesia, University of California, San Francisco.

‡ Professor and Chairman, Department of Anesthesiology and Intensive Care, Cochin Port-Royal University Hospital.

§ Professor and Chairman, Department of Anesthesiology and Intensive Care, Saint-Antoine University Hospital.

INDUCTION of general anesthesia increases cutaneous heat loss[1] and decreases metabolic heat production.[2] However, the rapid decrease in core temperature typically observed during the first hour of anesthesia cannot be explained simply by changes in total body heat balance. Instead, much of this hypothermia results from an internal core-to-peripheral redistribution of body heat.[1] Redistribution hypothermia does not trigger autonomic compensations during surgery, because general anesthesia impairs central thermoregulation.[3–5]

The calcium-channel blocker nifedipine is an arterial vasodilator that presumably increases cutaneous heat loss. Therefore, in a preliminary study, we tested the hypothesis that vasodilation induced by chronic nifedipine treatment would decrease intraoperative core temperature relative to an untreated control group.[6] Surprisingly, the treated patients developed considerably *less* hypothermia than those in the control group. Further reflection indicated that initial hypothermia in patients chronically given nifedipine may have been prevented because they already were vasodilated.

Drug-induced vasodilation would facilitate redistribution of core heat to peripheral tissues. Core temperature, however, remains well regulated in the absence of anesthesia. Consequently, thermoregulatory responses would generate or conserve sufficient heat to maintain core temperature. After equilibration, the patient would be left vasodilated, with a small core-to-peripheral tissue temperature gradient. In this scenario, subsequent induction of general anesthesia would produce minimal redistribution hypothermia, because heat flow requires a temperature gradient.

A limitation of our preliminary study was that patients were not randomly assigned to nifedipine treatment. Consequently, it remains likely that the two groups were not entirely comparable, and that observed differences in core temperatures may have resulted from confounding factors, perhaps including the underlying pathology initially prompting nifedipine treatment. Furthermore, our previous study did not distinguish the effects of chronic nifedipine treatment from those produced by acute administration; just as vasodilation initiated well before induction of anesthesia may minimize redistribution hypothermia, similar vasodilation concurrent with anesthetic-induced vasodilation may augment the rate or magnitude of redistribution hypothermia. Accordingly, we tested the hypothesis that nifedipine treatment for 12 h before surgery would minimize intraoperative redistribution hypothermia, whereas nifedipine treatment immediately before induction of anesthesia would aggravate hypothermia.

Materials and Methods

With approval from our local Ethics Committee and informed consent, we studied 30 ASA Physical Status 1 and 2 patients undergoing elective total hip arthroplasty. None was obese, febrile, was taking vasodilators or medications likely to alter thermoregulation, or had a history of smoking, thyroid disease, dysautonomia, or Raynaud's syndrome.

Protocol

Patients were randomly assigned to one of three groups: (1) ten were given 20 mg long-acting nifedipine (Bayer, Munich, Germany) orally 12 h before surgery and 10 mg sublingually 1.5 h before surgery; (2) ten were given 10 mg sublingually just before induction of anesthesia; and (3) ten were not given nifedipine (control group).

All patients received 100 mg oral hydroxyzine 1 h before surgery. Anesthesia was induced by administration of 5 mg/kg sodium thiopental, 2 μg/kg fentanyl, and 0.1 mg/kg vecuronium. The patients' tracheas were intubated, and ventilation mechanically controlled to maintain end-tidal P_{CO_2} near 35 mmHg. The fresh gas flow was maintained at 2 l/min and administered *via* a semiclosed circle system without airway heating or humidification.

Anesthesia was maintained with fentanyl, isoflurane, and 60% nitrous oxide. Fentanyl was administered per clinical routine, in 50-μg increments, to treat increases in blood pressure. Supplemental vecuronium was administered as needed to maintain one to two twitches in response to supramaximal stimulation of the ulnar nerve at the wrist. At least 10 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} of fluid was given intravenously, and blood products were administered to maintain the hematocrit between 25 and 32%. All administered fluids were warmed to 37° C. Patients were not actively warmed during anesthesia, and passive insulation was restricted to a single layer of surgical drape.[7]

Monitoring

Ambient temperature was measured by a thermocouple positioned at the level of the patient, well away from any heat-producing equipment. Core temperature, before induction of anesthesia, was measured at the tympanic membrane. The aural probe was inserted until the patients felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when they easily detected a gentle rubbing of the attached wire. The probe was then securely taped in place and the aural canal was occluded with cotton. Tympanic membrane temperatures correlate well with distal esophageal temperatures during anesthesia.[8] After induction of anesthesia, core temperature was recorded from the distal esophagus.

Mean skin temperature was calculated from four sites: $0.3 \cdot (T_{chest} + T_{arm}) + 0.2 \cdot (T_{thigh} + T_{calf})$.[10] Fingertip blood flow was evaluated using the forearm minus fingertip, skin-surface temperature gradient. There is an excellent correlation between skin-temperature gradients and volume plethysmography.[11] All temperatures were measured using Mon-a-Therm thermometers and thermocouples (Mallinckrodt Anesthesiology Products, St. Louis, MO).

Heart rate was monitored continuously using three-lead electrocardiography. Blood pressure was determined oscillometrically at 5-min intervals. Respiratory

gas concentrations were quantified using a calibrated end-tidal gas analyzer (Datex Medical Instrumentation, Helsinki, Finland). All other data were recorded at 10-min intervals, starting immediately before induction of anesthesia ("initial" values).

Data Analysis

As in previous studies,[12,13] we considered a gradient of 4° C to indicate significant thermoregulatory vasoconstriction. The distal esophageal temperature triggering significant vasoconstriction was considered to be the thermoregulatory threshold.

Data such as blood pressure and end-tidal isoflurane concentrations were recorded at the specified intervals and then averaged, first within each patient and then within each group. Morphometric data and results in the two treatment groups were compared to values in the control patients using a one-way ANOVA and Dunnitt's or Student–Newman–Keuls tests. As recommended by Mathews et al.,[14] core and mean skin temperatures in each group after 60 and 130 min of anesthesia were compared using one-way ANOVA. All values are expressed as means ± SD; differences were considered significant when $P < 0.05$.

Results

The gender, age, weight, and height of the patients in each group did not differ significantly. The ambient

Table 1. Morphometric and Anesthetic Data

	Control	PM/AM	Preinduction
Age (yr)	61 ± 14	64 ± 7	62 ± 13
Weight (kg)	70 ± 12	70 ± 13	65 ± 7
Height (cm)	165 ± 6	161 ± 9	160 ± 11
Gender (M/F)	4/6	5/5	6/4
Ambient temperature (° C)	18.9 ± 1.5	18.4 ± 1.4	18.8 ± 1.4
End-tidal isoflurane (%)	0.9 ± 0.4	1.1 ± 0.4	1.0 ± 0.5
Administered fentanyl (μg)	255 ± 72	130 ± 63	194 ± 50
Fluid replacement (l)	2.4 ± 0.6	2.0 ± 0.5	2.1 ± 0.3

Results are expressed as means ± standard deviations.

Age, weight, height, gender, ambient temperature, end-tidal isoflurane concentration, and volume of administered fluid did not differ significantly from those in the control group in the patients given nifedipine both the night before and the morning of surgery (PM/AM) or in those given nifedipine immediately before induction of anesthesia (preinduction). The administered fentanyl doses differed significantly in all three groups; however, the differences were not clinically important.
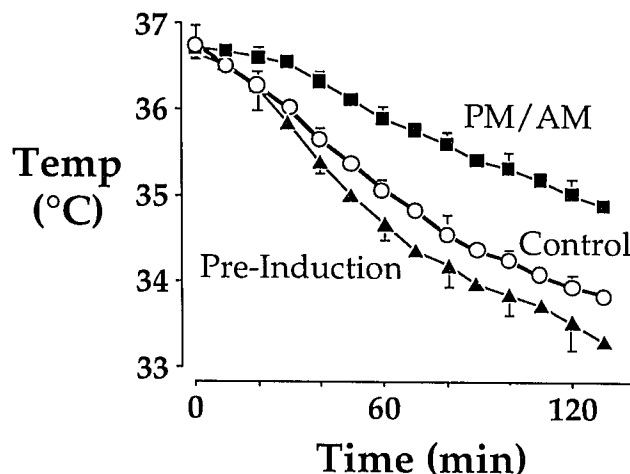

Fig. 1. Intraoperative core temperature decreased most in patients given nifedipine only immediately before induction of anesthesia (Preinduction) and least in those given nifedipine both the night before and the morning of surgery (PM/AM). The core temperatures at 60 and 130 elapsed min differed significantly in each of the three groups. Data are presented as mean ± SD.

operating room temperature, end-tidal isoflurane concentration, and fluid replacement volume also did not differ significantly in the three groups. The administered fentanyl doses differed significantly in all three groups, but the differences were not clinically important (table 1). Surgery lasted at least 130 min in each patient.

The heart rate and blood pressure were similar in the three groups. Preinduction core temperature was also similar in the three groups. Vasoconstriction occurred in only two patients during the study, and both were in the group that was given nifedipine immediately before induction of anesthesia. Vasoconstriction occurred after 90 and 110 min of anesthesia, at core temperatures of 34.6 and 35.2° C, respectively.

During the first hour of anesthesia, core temperature decreased significantly less in the patients given nifedipine both the night before and the morning of surgery than in the control group. In contrast, core temperature decreased significantly more in the patients given nifedipine immediately before induction of anesthesia than in the control patients. Consequently, the decreases in core temperature in each of the treatment groups differed significantly 1 h after induction. During the subsequent 70–130 min of anesthesia, core temperature decreased at comparable rates in each group (fig. 1). Core temperature in the two nifedipine-treated

groups differed by 1.2° C after 60 min of anesthesia, and by 1.6° C after 130 min.

Initial mean skin-surface temperature was less in the control patients than in the other two groups, but the difference was not statistically significant. During surgery, skin temperatures were comparable in the two treatment groups, and significantly higher than those in the control patients (table 2).

Discussion

Intraoperative hypothermia is common and potentially dangerous.[15–19]‖ It typically develops in three phases: (1) an initial rapid decrease in core temperature, largely caused by an internal core-to-peripheral redistribution of body heat;[1] (2) a slower, linear decrease in core temperature, apparently resulting when heat loss exceeds metabolic heat production;[20] and (3) a core temperature plateau resulting from decreased cutaneous heat loss[5] and constraint of metabolic heat to the core thermal compartment,[21] observed in patients becoming sufficiently hypothermic to trigger thermoregulatory vasoconstriction.[13,22]

The importance of redistribution hypothermia is illustrated by studies in which cutaneous warming is administered only *before* induction of anesthesia. Such warming minimally alters core temperature (which remains well regulated), but does increase peripheral tissue temperature and total body heat content. The resulting small core-to-periphery temperature gradient minimizes redistribution hypothermia when general anesthesia is subsequently induced.[23,24]

A similar mechanism apparently minimized hypothermia in the patients given nifedipine both the night before and the morning of surgery. In this case, vasodilation induced by nifedipine well before induction of anesthesia reduced the core-to-peripheral tissue temperature gradient. Subsequent redistribution was then minimal, because heat flow requires a temperature gradient. The temperature difference between this group and the control patients was 0.8° C after 60 min of anesthesia, and 1.1° C after 130 min. These temperature differences are probably sufficient to provoke hypothermia-related complications, including postoperative shivering.[25]

‖ Sheffield CW, Sessler DI, Hunt TK, Scheuenstuhl H: Mild hypothermia during halothane anesthesia decreases resistance to *S. Aureus* dermal infection in guinea pigs. Journal of Wound Healing and Regeneration (in press).

Table 2. Hemodynamic Data and Temperatures

	Control		PM/AM		Preinduction	
Heart rate (beats/min)	68	± 13	72	± 19	77	± 17
Mean blood pressure (mmHg)	100	± 17	97	± 19	99	± 16
Initial core temperature (° C)	36.8 ±	0.2	36.7 ±	0.2	36.7 ±	0.1
Initial skin temperature (° C)	32.3 ±	0.7	33.2 ±	1.0	33.0 ±	1.0
Hypothermia in 1st h (° C)	1.7 ±	0.2	0.8 ±	0.2	2.0 ±	0.2
Hypothermia from 70 to 120 min (° C)	1.0 ±	0.2	0.9 ±	0.2	1.1 ±	0.1
Core temperature after 60 min (° C)	35.1 ±	0.1	35.9 ±	0.1	34.7 ±	0.2
Skin temperature after 60 min (° C)	30.9 ±	0.8	32.0 ±	1.2	31.9 ±	0.6
Core temperature after 130 min (° C)	33.8 ±	0.1	34.9 ±	0.2	33.3 ±	0.3
Skin temperature after 130 min (° C)	30.6 ±	1.0	31.6 ±	1.0	31.3 ±	0.6

Values are expressed as means ± standard deviations.

The decrease in core temperature during the 1st h of surgery, the core temperature at 60 elapsed min, and the core temperature after 130 min differed significantly in each of the three groups. After 60 min of anesthesia, skin temperatures were significantly less in the control patients than in the two treatment groups; after 130 min of anesthesia, only control and preinduction values differed significantly. The rate at which hypothermia developed during the 2nd h of surgery was similar in all three groups.

In distinct contrast to the patients given nifedipine both the night before and the morning of surgery, those given the drug only immediately before induction of anesthesia became significantly more hypothermic than the control patients. These data indicate that nifedipine-induced vasodilation combined with isoflurane-induced vasodilation to aggravate redistribution hypothermia.

Independent of drug treatment, the amount of redistribution hypothermia depends critically on the initial core-to-peripheral tissue temperature gradient. Thus, core temperature differences produced by both nifedipine regimens probably would have been exaggerated had patients been maintained in a colder environment for several hours before induction of anesthesia. Conversely, less drug effect would be expected had the patients been maintained in a warmer environment before surgery.

The slow linear decrease in core temperature typically observed during the second through fourth hour of anesthesia results from heat loss exceeding metabolic heat production.[20] There is no evidence that nifedipine

directly influences metabolic heat production, and it is unlikely to do so based on its known pharmacology. Furthermore, nonshivering thermogenesis does not contribute to heat balance in anesthetized adults.[26] Consequently, it is not surprising that core temperature in each of our three treatment groups decreased at roughly comparable rates during this period.

Intraoperative heat balance is a function of cutaneous radiative and convective loss, and of evaporative loss from surgical incisions,[27] both of which are strongly influenced by ambient temperature.[28] The rate at which core temperature decreased in our patients during the second hour of anesthesia would, thus, have been greater had the ambient temperature been less or the surgical procedures larger. However, the cooling rate probably would have remained comparable in the three groups.

Thermoregulatory vasoconstriction would not be expected in patients given $\approx 1\%$ isoflurane, 60% nitrous oxide, and fentanyl, and was only observed in 2 of the 30 patients. Nifedipine is a more potent smooth muscle dilator than verapamil or diltiazem.[29] It is, therefore, likely that these other calcium-channel antagonists would alter heat balance less.

Blood pressures and heart rates were comparable in our three treatment groups. The lack of clinically important hemodynamic effect noted in our anesthetized patients is typical. Similarly, we have previously shown that intraoperative thermoregulatory vasoconstriction does not significantly increase mean arterial blood pressure or decrease heart rate,[5] and we observed no such effect in these patients.

Our patients were randomly assigned to one of the three groups, but study personnel were not blinded to treatment. Although differences in applied passive insulation could, potentially, influence intraoperative core temperature, insulation was strictly limited by protocol to a single layer of surgical drape. Because the major factor influencing core temperature during the first hour of anesthesia is internal redistribution of body heat,[1] even active warming is nearly ineffective during this period.[20] Thus, subtle differences in applied insulation are unlikely to explain observed objective differences among the groups.

The amount of fentanyl administered intraoperatively was not strictly controlled, and did differ significantly among the groups. However, the differences between the groups given the highest and lowest doses was only 125 μg—a dose that few clinicians would consider clinically important over a 2-h period. Fentanyl has no

direct vascular effects, but does decrease the threshold for vasoconstriction.[13] Thermoregulatory vasoconstriction during isoflurane anesthesia decreases cutaneous heat loss[5] and constrains metabolic heat to the thermal core.[21] Differences in administered fentanyl doses might, therefore, have been important if vasoconstriction occurred in large numbers of patients in one group. However, vasoconstriction was observed in only two patients in the entire study, and both were in the group that was given an intermediate dose of fentanyl.

In summary, vasodilation induced by nifedipine well before induction of anesthesia minimized redistribution hypothermia, presumably by decreasing the core-to-peripheral tissue temperature gradient. In contrast, redistribution hypothermia was aggravated by administration of the same drug immediately before induction of anesthesia. Drug-induced modulation of vascular tone thus produces clinically important alterations in intraoperative core temperature.

References

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

2. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 35:8–16, 1971

3. Hynson JM, Sessler DI, Belani K, Washington D, McGuire J, Merrifield B, Schroeder M, Moayeri A, Crankshaw D, Hudson S: Thermoregulatory vasoconstriction during propofol/nitrous oxide anesthesia in humans: Threshold and Sp_{O2}. Anesth Analg 75:947–952, 1992

4. Washington DE, Sessler DI, McGuire J, Hynson J, Schroeder M, Moayeri A: Painful stimulation minimally increases the thermoregulatory threshold for vasoconstriction during enflurane anesthesia in humans. ANESTHESIOLOGY 77:286–290, 1992

5. Sessler DI, Hynson J, McGuire J, Moayeri A, Heier T: Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases heat loss. ANESTHESIOLOGY 76:670–675, 1992

6. Vassilieff N, Rosencher N, Deriaz H, Conseiller C, Lienhart A: Effects de la nifédipine en prémédication sur l'hypothermia peropératoire. Ann Fr Anesth Reanim 11:484–487, 1992

7. Sessler DI, McGuire J, Sessler AM: Perioperative thermal insulation. ANESTHESIOLOGY 74:875–879, 1991

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

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

10. Ramanathan NL: A new weighting system for mean surface temperature of the human body. J Appl Physiol 19:531–533, 1964

11. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. ANESTHESIOLOGY 73: 541–545, 1990

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

13. Sessler DI, Olofsson CI, Rubinstein EH: The thermoregulatory threshold in humans during nitrous oxide-fentanyl anesthesia. ANESTHESIOLOGY 69:357–364, 1988

14. Matthews JNS, Altman DG, Campbell MJ, Royston P: Analysis of serial measurements in medical research. BMJ 300:230–235, 1990

15. Sessler DI, Rubinstein EH, Moayeri A: Physiological responses to mild perianesthetic hypothermia in humans. ANESTHESIOLOGY 75: 594–610, 1991

16. Just B, Delva E, Camus Y, Lienhart A: Oxygen uptake during recovery following naloxone. ANESTHESIOLOGY 76:60–64, 1992

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

18. Valeri CR, Khabbaz K, Khuri SF, Marquardt C, Ragno G, Feinhold H, Gray AD, Axford T: Effect of skin temperature on platelet function in patients undergoing extracorporeal bypass. J Thorac Cardiovasc Surg 104:108–116, 1992

19. Carli F, Emery PW, Freemantle CAJ: Effect of perioperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. Br J Anaesth 63:276–282, 1989

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

21. 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 78: 856–863, 1993

22. Bissonnette B, Sessler DI: Thermoregulatory thresholds for vasoconstriction in pediatric patients anesthetized with halothane or halothane and caudal bupivacaine. ANESTHESIOLOGY 76:387–392, 1992

23. Hynson JM, Sessler DI, Moayeri A, McGuire J, Schroeder M: The effects of preinduction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia. ANESTHESIOLOGY 79: 219–228, 1993

24. Just B, Trévien V, Delva E, Lienhart A: Prevention of intraoperative hypothermia by preoperative skin-surface warming. ANESTHESIOLOGY 79:214–218, 1993

25. Lienhart A, Fiez N, Deriaz H: Frisson postopératoire: Analyse des principaux facteurs associés. Ann Fr Anesth Reanim 11:488–495, 1992

26. Hynson JM, Sessler DI, Moayeri A, McGuire J: Absence of non-shivering thermogenesis in anesthetized humans. ANESTHESIOLOGY 79: 695–703, 1993

27. Roe CF: Effect of bowel exposure on body temperature during surgical operations. Am J Surg 122:13–15, 1971

28. Sessler DI, Sessler AM, Hudson S, Moayeri A: Heat loss during surgical skin preparation. ANESTHESIOLOGY 78:1055–1064, 1993

29. Roizen MF: Anesthetic implications of concurrent diseases, Anesthesia. 3rd edition. Edited by Miller RD. New York, Churchill Livingstone, 1990, pp 793–893