

The Thermoregulatory Threshold in Humans during Nitrous Oxide-Fentanyl Anesthesia

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Narcotics and nitrous oxide (N_2O) inhibit thermoregulatory responses in animals. The extent to which N_2O /fentanyl anesthesia lowers the thermoregulatory threshold in humans was tested by measuring peripheral cutaneous vasoconstriction using skin-surface temperature gradients (forearm temperature-fingertip temperature) and the laser Doppler perfusion index. Fifteen unpremedicated patients were anesthetized with N_2O (70%) and fentanyl ($10 \mu\text{g}/\text{kg}$ iv bolus followed by $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ infusion) during elective, donor nephrectomy. Patients were randomly assigned to undergo additional warming (humidified respiratory gases, warmed intravenous fluids, and a heating blanket over the legs; $n = 5$) or standard temperature management (no special warming measures; $n = 10$). Significant vasoconstriction was prospectively defined as a skin-surface temperature gradient between forearm surface and fingertip surface $\geq 4^\circ \text{C}$, and the thermoregulatory threshold was defined as the esophageal temperature at which such vasoconstriction occurred. Vasoconstriction did not occur in the patients who received additional warming and thus remained nearly normothermic [average minimum esophageal temperature = $35.8 \pm 0.4^\circ \text{C}$ (SD)] but did in six hypothermic patients at a mean esophageal temperature of $34.2 \pm 0.5^\circ \text{C}$. Four hypothermic patients developed a passive thermal steady state without becoming sufficiently cold to trigger vasoconstriction. Thus, active thermoregulation occurs during N_2O /fentanyl anesthesia but does not occur until core temperatures are $\sim 2.5^\circ \text{C}$ lower than normal. The thermoregulatory threshold during N_2O /fentanyl anesthesia is similar to that previously determined during halothane ($34.4 \pm 0.2^\circ \text{C}$). Bupivacaine 0.5% (1.5 ml) injected around the base of the fourth finger prevented vasoconstriction, indicating that intraoperative vasoconstriction can be prevented by local neural blockade (as can normal thermoregulatory vasoconstriction). Decreased skin-surface temperatures occurred primarily in the fingers, whereas the adjacent palms were largely spared. This pattern is similar to that produced by normal thermoregulatory vasoconstriction and is consistent with the known distribution of thermoregulatory arteriovenous shunts. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl. Brain: hypothalamus. Hypothermia. Temperature, measurement: esophageal; skin.)

HYPOTHERMIA produces thermoregulatory vasoconstriction in patients anesthetized with halothane¹ and isoflurane,² but the response thresholds are $\sim 2.5^\circ \text{C}$ below normal. Both narcotics^{3,4} and nitrous oxide^{5,6} (N_2O) inhibit thermoregulatory responses in animals. Thus, we tested the hypothesis that N_2O /fentanyl anesthesia decreases the thermoregulatory threshold in humans.

To further characterize intraoperative thermoregulatory vasoconstriction we: 1) compared the decrease in cutaneous capillary (nutritional) blood flow with the decrease in arteriovenous shunt (thermoregulatory) flow; 2) used a local anesthetic nerve blockade to evaluate the contribution of circulating factors; and 3) qualitatively measured the spatial distribution of vasoconstriction to determine whether it matched the anatomic distribution of thermoregulatory arteriovenous shunts.

Methods

With approval from the University of California Committee on Human Research and written, informed consent, we studied 15 unpremedicated, ASA P.S. I patients who electively donated one kidney to a relative. None was obese, taking medication, or had a history of thyroid disease, dysautonomia, Raynaud's syndrome, or malignant hyperthermia. All operations began between 8:00 AM and 1:00 PM. Anesthesia was induced by inhalation of halothane 2-4%, nitrous oxide 70%, and oxygen for ~ 10 min; thiopental was not administered. Vecuronium ($0.1 \text{ mg}/\text{kg}$ iv) was administered and the tracheas of all patients intubated.

Anesthesia was maintained during surgery with N_2O (70%) and fentanyl, using a total fresh gas flow of 5 l/min (no halothane was administered after intubation). Fentanyl, $10 \mu\text{g}/\text{kg}$, was given iv during the first 30 min of anesthesia followed by an infusion at a rate of $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Additional fentanyl (50 mg) was administered iv, as needed, to maintain diastolic blood pressure below 95 mmHg. Muscle relaxation was provided, as needed, to maintain a 1-2 twitch mechanical response to train-of-four stimulation of the median nerve by a peripheral nerve stimulator, by administration of additional vecuronium. To maintain optimal renal function during surgery, each donor was given ~ 5 l lactated Ringer's solution intraoperatively. Furosemide (20 mg) and mannitol (25 g) also were administered. Each oper-

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ation was performed by one of three surgeons using similar surgical techniques.

Patients were randomly assigned to receive standard temperature management (no hypothermia precautions) or to receive additional warming measures, including warm iv fluids, breathing circuit humidification, and a warming blanket placed over the legs. The fluid warmer, humidifier, and warming blanket were each thermostatically controlled at 37° C. The operating room was maintained at a normal temperature ($\approx 21^\circ\text{C}$) for all patients to provide similar cutaneous input to the thermoregulatory system in both groups. Cutaneous input was not identical, however, because heating blankets covered the legs of the nearly normothermic patients.

Core temperatures were measured using disposable Mon-a-Therm® (St. Louis, Missouri) thermocouples incorporated into esophageal stethoscopes. Position in the distal esophagus was adjusted to maximize heart tones. The accuracy and precision of these thermocouples and this placement technique have been documented previously.⁷

Thermoregulatory vasoconstriction was evaluated using skin temperature gradients, which were calculated by subtracting fingertip surface temperature from forearm surface temperature. To measure skin-surface temperatures, disposable, self-sticking Mon-a-Therm® thermocouples were attached to each patient's nondependent arm, which was positioned at the level of the right atrium. Mon-a-Therm® skin-surface probes are self-sticking disks $\approx 1\text{ cm}$ in diameter. The forearm thermocouple was placed on the radial side of the arm midway between the wrist and the elbow; the fingertip probe was positioned on the tip of the index finger opposite the nail bed. As in our previous study,¹ significant vasoconstriction was prospectively defined as a skin temperature gradient $\geq 4^\circ\text{C}$. The thermoregulatory threshold was defined as the esophageal temperature at which the skin-temperature gradient first exceeded 4°C . The monitored arm did not have an iv catheter or blood pressure cuff, and all thermocouple sites were fully exposed to room air.

The effect of neural blockade on the temperature gradient was evaluated by infiltrating 1.5 ml of bupivacaine 0.5% without epinephrine subcutaneously into four sites around the base of the fourth finger on the nondependent arm. The temperature of this finger was compared with that of the index finger 30 min before, and 30 min after vasoconstriction (forearm-index finger gradient = 4°C).

Peripheral vasoconstriction also was evaluated using a Periflux® 3 (Medex Inc., Hilliard, Ohio) laser Doppler monitor. This device provides a perfusion index based on the number and velocity of red blood cells in the

outer 1 mm of skin. Perfusion determined using the laser Doppler correlates well with ^{133}Xe washout⁸ and dynamic capillaroscopy.⁹ We positioned the fiberoptic laser probe perpendicular to the skin opposite the nailbed on the second finger of the nondependent arm.

Spatial distribution of thermoregulatory vasoconstriction was evaluated by simultaneously measuring six skin-surface temperatures in two hypothermic and two nearly normothermic patients. The additional skin thermocouples were placed over the middle phalanx and proximal phalanx, on the palm near the thenar eminence, and on the midvolar portion of the wrist of each.

Skin-surface and esophageal temperatures, laser Doppler perfusion index, end-tidal halothane concentration, and blood pressure were recorded every 10 min from induction until closure of the surgical incision. Following closure, intraoperative and postoperative management were determined by the attending anesthesiologist. Continuous variables were analyzed using paired or unpaired Student's *t* test as appropriate. Quantile data were analyzed using the log-likelihood ratio.¹⁰ Differences were considered significant when $P < 0.05$.

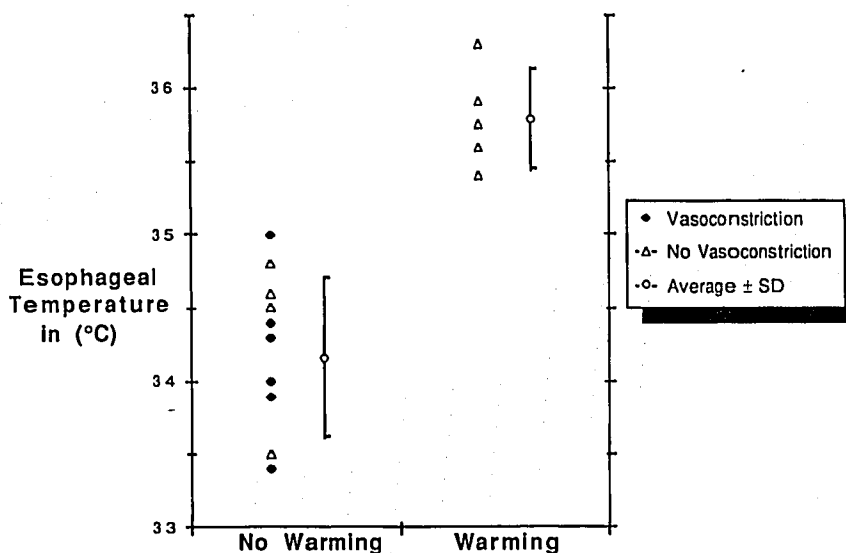
Results

The ten patients anesthetized without the protocol warming maneuvers reached a mean lowest esophageal temperature of $34.3 \pm 0.5^\circ\text{C}$ (SD). In contrast, the five patients actively warmed remained nearly normothermic with a mean lowest esophageal temperature of $35.8 \pm 0.4^\circ\text{C}$ ($P < 0.05$). Skin-surface temperature gradients were $< 1^\circ\text{C}$ in all actively warmed patients and became $\geq 4^\circ\text{C}$ in 6 of 10 hypothermic patients ($P < 0.05$). Vasoconstriction in hypothermic patients occurred between 100 and 190 min following induction of anesthesia [$167 \pm 33\text{ min}$ (SD)]. Once vasoconstriction occurred, skin temperature gradients remained $\geq 4^\circ\text{C}$ for the duration of surgery. Six hypothermic patients demonstrated significant vasoconstriction at esophageal temperatures between 33.4°C and 35.0°C (average: $34.2 \pm 0.5^\circ\text{C}$, SD) (fig. 1).

A skin-temperature gradient $\geq 4^\circ\text{C}$ correlated with a decrease in the laser Doppler perfusion index (figs. 2 and 3). Changes in the perfusion index are presented as a percentage of the control value because the raw values varied considerably among patients. The correlation between the perfusion index and the skin-surface temperature gradient is illustrated in figure 4. The regression equation is: Perfusion = $-7.9 \times \text{Gradient} + 67$, $r^2 = 0.63$.

Temperatures of the fourth fingers anesthetized with bupivacaine were significantly higher than those of the index fingers of the same hand 30 min before vasocon-

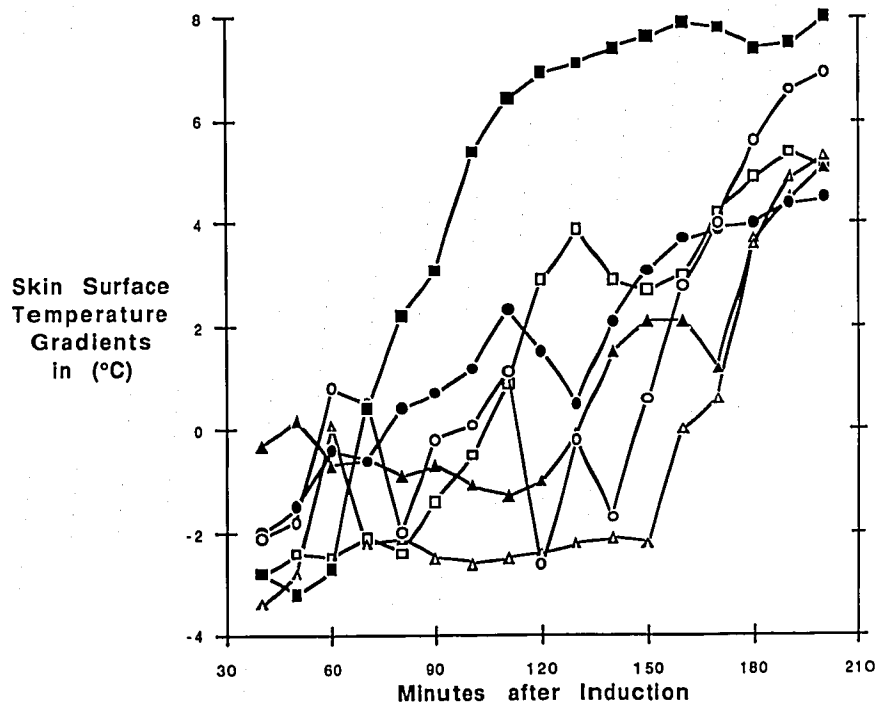
FIG. 1. Significant vasoconstriction was observed in six of ten elective kidney donors who became hypothermic during anesthesia and surgery with N₂O/fentanyl (left). Vasoconstriction did not occur in five other patients maintained normothermic (right). Thermoregulatory vasoconstriction was prospectively defined as a skin-surface temperature gradient (forearm temperature-fingertip temperature) $\geq 4^{\circ}\text{C}$. The thermoregulatory threshold (the esophageal temperature at which the skin-temperature gradient first exceeds 4°C) during N₂O/fentanyl anesthesia is $34.2 \pm 0.5^{\circ}\text{C}$ (SD).



striction ($31.9 \pm .9^{\circ}\text{C}$ vs. $28.4 \pm 1.7^{\circ}\text{C}$). Fourth-finger temperatures in normothermic patients and in hypothermic patients in whom vasoconstriction did not occur were $\approx 3^{\circ}\text{C}$ higher than the temperatures of the corresponding index fingers. Index-finger temperatures decreased by $\approx 5^{\circ}\text{C}$ to $23.4 \pm .9^{\circ}\text{C}$ during vasoconstriction, whereas temperature in fourth fingers anesthetized with bupivacaine decreased $< 1^{\circ}\text{C}$ to $31.2 \pm 1.2^{\circ}\text{C}$. The temperature decreases in both fingers were statistically significant but sevenfold less in fingers anesthetized with bupivacaine.

Index- and fourth-finger temperature changes 30 min before and 30 min after vasoconstriction appear in figure 5. Data for only five patients are presented because one hypothermic patient in whom vasoconstriction subsequently occurred refused bupivacaine infiltration. Increased skin-surface temperature gradients resulted primarily from decreased fingertip temperature. In all patients, forearm skin temperatures were $\approx 3.5^{\circ}\text{C}$ below esophageal temperatures. This was in marked contrast to fingertip temperatures, which frequently decreased more than 8°C during the study.

FIG. 2. Skin-surface temperature gradients (forearm-fingertip) in six kidney donors who became hypothermic and vasoconstricted during N₂O/fentanyl anesthesia. Each patient is represented by a different symbol. Thermoregulatory vasoconstriction (prospectively defined as a gradient $\geq 4^{\circ}\text{C}$) was observed in each patient between 100 and 190 (167 \pm 33) min following induction of anesthesia. The average esophageal temperature at the time of vasoconstriction (thermoregulatory threshold) was $34.2 \pm 0.5^{\circ}\text{C}$ (SD).



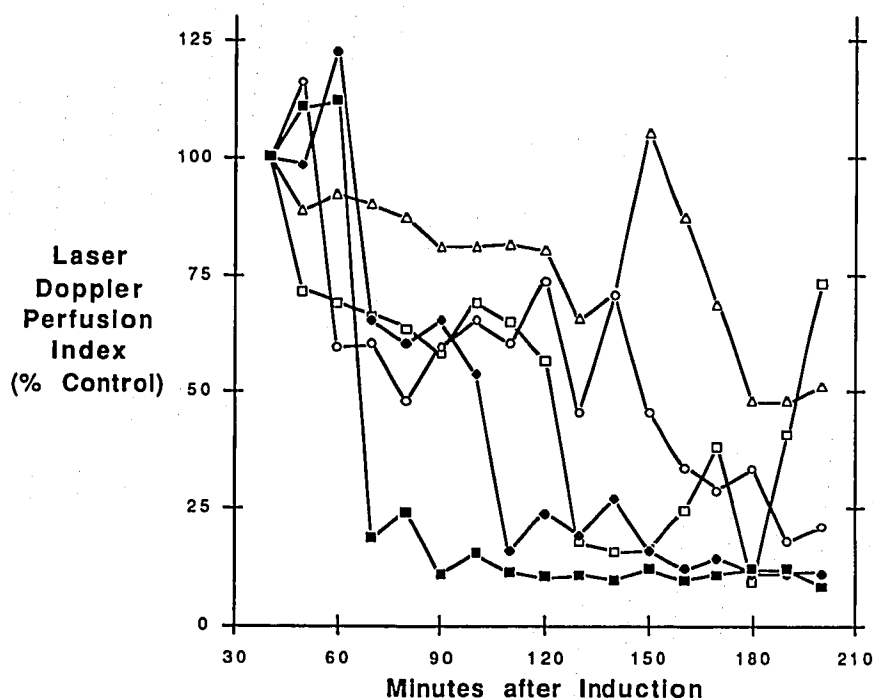


FIG. 3. Laser Doppler perfusion index in five of six kidney donors who became hypothermic and in whom vasoconstriction occurred during N_2O /fentanyl anesthesia. The data are presented as percent of the control because there was considerable interpatient variability in the raw values. Each patient is represented by a different symbol (the same symbols identify patients in fig. 2).

Vasoconstriction occurred primarily in the fingers, whereas hand, wrist, and forearm temperatures remained $\approx 3.5^\circ\text{C}$ below core temperature (fig. 6).

Ambient temperatures near the time of vasoconstriction were calculated for hypothermic patients who demonstrated significant vasoconstriction by averaging room temperatures recorded during the 30 min prior to and following vasoconstriction. The values recorded between 130 and 190 min following induction were averaged in normothermic patients and the hypothermic patients in whom vasoconstriction did not occur to

obtain ambient temperatures at comparable times. Ambient temperatures were not significantly different in the two groups ($20.3 \pm .8^\circ\text{C}$ vs. $21.0 \pm 0.5^\circ\text{C}$).

The ages of the hypothermic and normothermic patients did not differ significantly [40 ± 11 vs. 33 ± 6 yr (SD)]. There were five males and ten females; gender did not appear to affect the thermoregulatory threshold. The hypothermic patients required an average of $130\text{ }\mu\text{g}$ of additional fentanyl and the normothermic patients required an average $160\text{ }\mu\text{g}$ of additional fentanyl. There were no demographic differences or dif-

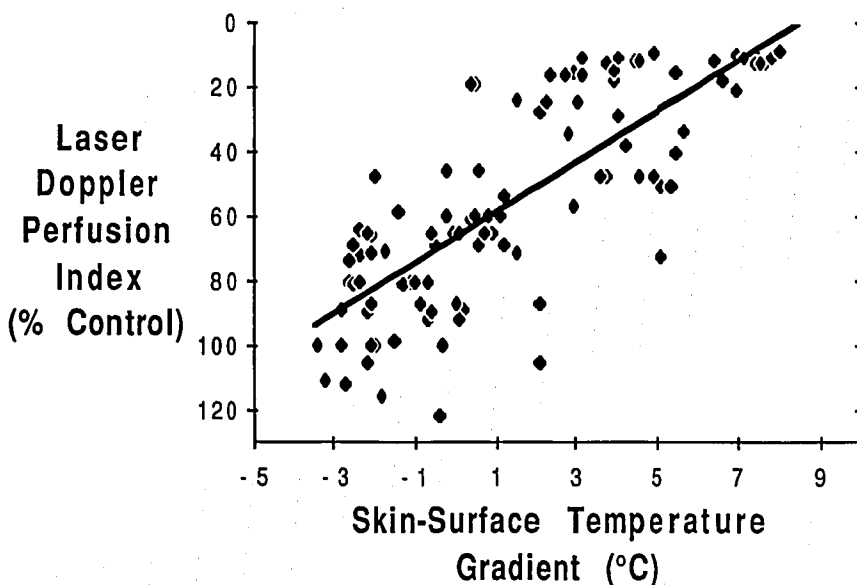
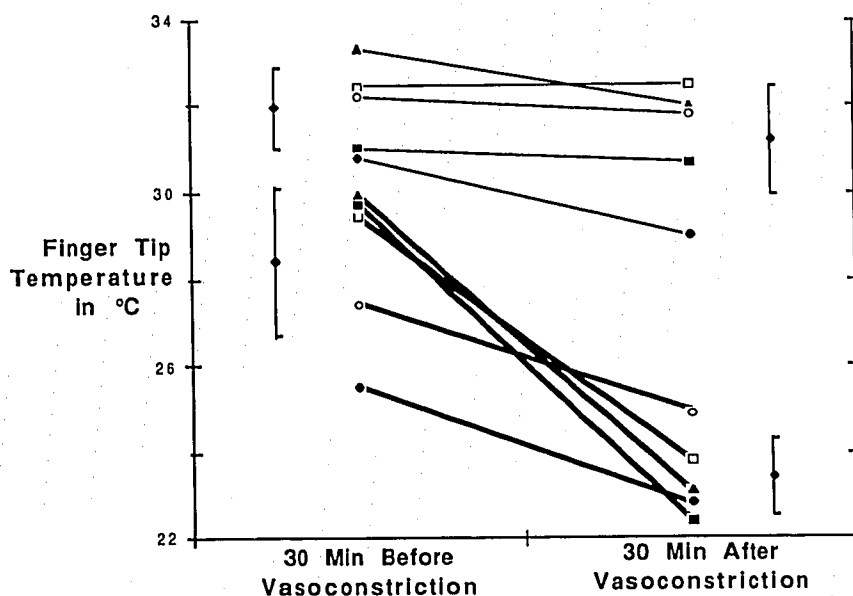


FIG. 4. Skin-surface temperature gradient is plotted against the laser Doppler perfusion index (percent of control). The regression equation is: $\text{Perfusion} = -7.9 \cdot \text{Gradient} + 67$, $r^2 = 0.63$.

FIG. 5. Changes in index- and fourth-finger temperatures from 30 min prior to vasoconstriction (forearm-index finger gradient = 4° C) to 30 min after constriction. Just after induction of anesthesia, bupivacaine (1.5 ml) was infiltrated subcutaneously into four sites around the base of the fourth finger to prevent neural transmission. Each symbol represents one patient. Temperatures of the index fingers are connected with thick lines and those of the fourth fingers with thin lines. The averages and SD for each group are indicated on the far right and far left sides of the figure. Both before and after vasoconstriction fourth-finger temperatures were significantly higher than index-finger temperatures. Temperatures of the index and fourth fingers decreased significantly during vasoconstriction but decreased seven times less in fingers injected with bupivacaine. This indicates that intraoperative, cold-induced vasoconstriction can be prevented by local neural blockade and is not caused by circulating factors.

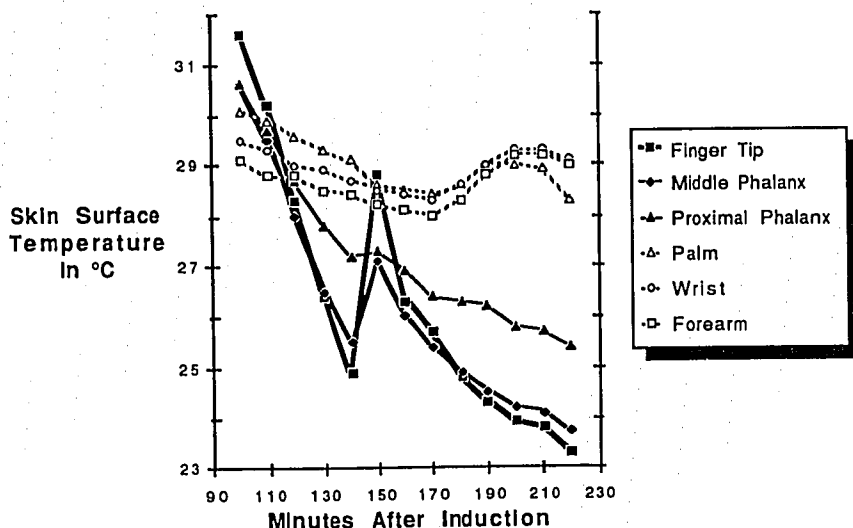


ferences in fentanyl administration between the hypothermic patients in whom vasoconstriction occurred and those in whom it did not. End-tidal halothane concentrations were <0.05% 30 min following induction of anesthesia. One normothermic patient was eliminated from the study 30 min after induction of anesthesia because intraoperative hypertension (175/116 mmHg) could not be controlled with additional fentanyl administration. No patient received a blood transfusion during surgery. Hypothermic patients did not become hypotensive or hypertensive at the time of vasoconstriction.

Discussion

Intraoperative hypothermia results from exposure to a cold environment, decreased metabolic rate, and anesthetic-induced inhibition of thermoregulation. Surgical patients are commonly believed to be poikilothermic.¹¹ However, recent studies demonstrate that thermoregulatory responses do occur when patients become sufficiently hypothermic.^{1,2} The only thermoregulatory responses available to anesthetized and paralyzed hypothermic patients are nonshivering thermogenesis (increased metabolic heat production)¹² and cutaneous va-

FIG. 6. Skin-surface temperatures at six sites on the nondependent arm of one patient during vasoconstriction. Temperature of the entire finger decreased substantially, whereas palm-, wrist-, and forearm-temperatures changed little. Fingertip temperature was initially highest, became lowest at 140 min, again became highest during a brief reversal of the gradient at 150 min, and finally reached 8° C lower than its initial temperature. This pattern illustrates the magnitude of thermoregulatory vasoconstriction and the rapidity with which skin temperatures change. Cold-induced intraoperative vasoconstriction occurs primarily in the fingers, which is a spatial pattern similar to that produced by normal thermoregulatory vasoconstriction and is consistent with the known distribution of anatomic, thermoregulatory arteriovenous shunts.



soconstriction (decreased environmental heat loss).¹³ Only vasoconstriction was evaluated in this study because nonshivering thermogenesis is not thought to be important in adult humans.^{1,12}

Anatomic arteriovenous shunts are concentrated in the fingers and toes; therefore, blood flow to distal extremities is affected more by thermoregulation than is flow to central skin.¹⁴ As in our previous studies, we measured skin-surface temperature gradients (forearm temperature–fingertip temperature) to evaluate vasoconstriction during surgery.¹ This method of measurement is noninvasive, inexpensive, and correlates well with other methods of determining cutaneous blood flow, including plethysmography.¹⁵

During N₂O/fentanyl anesthesia, significant vasoconstriction was not detected in any patient who remained normothermic. However, vasoconstriction was observed in six of ten hypothermic patients at esophageal temperatures between 33.4° C and 35.0° C (34.2 ± 0.5° C). This finding is consistent with observations in animals that both narcotics^{3,4} and N₂O^{5,6} inhibit thermoregulatory responses. The thermoregulatory threshold (core temperature at which vasoconstriction occurs) during N₂O/fentanyl anesthesia was similar to that during halothane/oxygen (34.4 ± 0.2° C). Although the thermoregulatory thresholds were similar during N₂O/fentanyl and halothane/oxygen anesthesia, the threshold temperature range (1.6° C *vs.* 0.8° C) and the SD [0.5 (n = 6) *vs.* 0.2 (n = 5)] were greater during N₂O/fentanyl anesthesia. These findings are consistent with the known, large, interpatient variability in response to opiates.

In four of ten hypothermic patients given N₂O/fentanyl vasoconstriction did not occur, whereas it occurred in all hypothermic patients receiving halothane.¹ These four probably reached a passive thermal steady state (constant core temperature without vasoconstriction). Passive steady state is common during procedures that produce minimal environmental heat loss and occurs when metabolic heat production equals heat loss to the environment without core temperature being sufficiently low to trigger thermoregulatory responses.¹⁶ Three hypothermic patients in whom vasoconstriction did not occur had relatively high minimum esophageal temperatures (34.5–34.8° C) compared with those in whom vasoconstriction did occur. Another did not vasoconstrict despite an esophageal temperature of 33.5° C, but one patient required a core temperature of 34.4° C to trigger vasoconstriction.

The only central temperature we measured was in the distal esophagus. Previous studies have demonstrated a high correlation between this temperature and that of other deep-body sites (*e.g.*, hypothalamus, rectum) in

patients not undergoing cardiopulmonary bypass.⁷ Thus, esophageal temperature can be considered typical of thermal inputs from most deep tissues. Animal studies indicate that deep tissues (including the neuroaxis) account for ≈80% of thermoregulatory input^{17–20} and skin-surface temperature contributes the rest.^{21,22} Hypothalamic temperature *per se* contributes only ≈20%.^{23,24} Thermal input from the skin was similar in both groups because ambient temperatures were similar in all patients. (Thermal input was not, however, identical because a warming blanket was placed over the legs of the normothermic patients.)

The nonanesthetic drugs administered to these patients, furosemide, mannitol, and vecuronium, are not believed to have any effects on thermoregulation. We did not administer barbiturates because they may inhibit thermoregulation.²⁵ A limitation of this study is that we compared our current results with those obtained previously. However, our previous study used similar methods and evaluated patients of a similar age undergoing similar surgery. Thus, we believe these comparisons to be valid, although the studies were not concurrent.

Total digital skin blood flow is divided into arteriovenous shunt (thermoregulatory) and capillary (nutritional) components.^{26,27} Skin-surface temperature gradients are determined by total flow (which is largely shunt), whereas the laser Doppler measurement detects primarily capillary flow (in the outer 1 mm of the skin). Thermoregulatory vasoconstriction is believed to occur primarily in the cutaneous arteriovenous shunts.²⁸ Nonetheless, we found that increased gradients correlated well with a decreased laser Doppler perfusion index. The laser index did demonstrate greater intrapatient and interpatient variability and is considerably more expensive than skin-surface temperature measurements using thermocouples.

Neural blockade following bupivacaine injection around the base of the finger increased fingertip temperature in normothermic patients and in hypothermic patients prior to vasoconstriction. Some vascular tone was therefore present even when core temperatures were well above the thermoregulatory threshold. We have yet to evaluate hyperthermic patients to determine whether increasing core temperature causes further vasodilation.

Although temperatures of the neurally blocked fingers decreased during thermoregulatory vasoconstriction, the decrease was small compared with that of the unblocked fingers. Intraoperative vasoconstriction (although presumably centrally mediated) is therefore under local neural control, as is normal thermoregulatory vasoconstriction. In unanesthetized animals ther-

moregulatory vasoconstriction is mediated by sympathetic nerves.^{29,30} Surgical stress and vascular volume fluxes can cause vasoconstriction by increasing circulating catecholamine concentrations, but vasoconstriction was not detected in normothermic patients. The small temperature decrease in the blocked fingers may have resulted from circulating catecholamines released in association with nonshivering thermogenesis.¹²

Anatomic, thermoregulatory arteriovenous shunts are located primarily in the fingers and toes.¹⁴ Consequently, thermoregulatory vasoconstriction in unanesthetized humans occurs primarily in the distal extremities.³¹ In the hypothermic patients we studied, skin temperatures primarily decreased in the fingers, whereas the adjacent palm was relatively spared. Thus, the spatial pattern of cold-induced vasoconstriction in anesthetized patients is similar to that produced by normal thermoregulatory vasoconstriction. It is likely that a more intense cold stimulus would produce more proximal vasoconstriction.

The skin-temperature gradients usually increase smoothly once vasoconstriction starts. However, a partially established gradient can be temporarily reversed by increasing anesthetic dose, which presumably decreases the threshold.¹ Temporary reversals also may result from unrecorded temperature changes (*e.g.*, those inside the surgical incision) that increase total thermoregulatory input to a level above that which triggers vasoconstriction. Although we were unable to determine the etiology of one such reversal (*fig. 6*), it does confirm that finger temperature can both decrease and increase rapidly. This indicates the sensitivity of skin temperature gradient measurements and that vasodilation, as well as vasoconstriction, can be easily detected when it occurs.

In summary, active thermoregulation occurred during N₂O/fentanyl anesthesia, but did not occur until core temperatures were $\approx 2.5^\circ\text{C}$ below normal. The thermoregulatory threshold during N₂O/fentanyl anesthesia ($34.2 \pm 0.5^\circ\text{C}$) was similar to that during halothane/oxygen ($34.4 \pm 0.2^\circ\text{C}$). Neural blockade prevented hypothermia-induced vasoconstriction, suggesting that intraoperative vasoconstriction is mediated by the sympathetic nervous system (not circulating factors), as is thermoregulatory vasoconstriction in unanesthetized humans. Additionally, vasoconstriction occurred primarily in the fingers, which conforms to the anatomic location of the thermoregulatory arteriovenous shunts.

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