The Thermoregulatory Threshold is Inversely Proportional to Isoflurane Concentration

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This study tested the hypothesis that the threshold for thermoregulatory vasoconstriction is lowered as isoflurane concentration increases, but that the intensity of vasoconstriction, once triggered, is well preserved during isoflurane anesthesia. The thermoregulatory threshold was prospectively defined as the central temperature at which vasoconstriction occurred, and significant vasoconstriction was defined as a skin-surface temperature gradient (forearm–fingertip) ≥ 4°C. The threshold for thermoregulatory vasoconstriction and the intensity of vasoconstriction, measured as maximum skin-temperature gradient, was determined in six unpremedicated patients electively donating a kidney during isoflurane anesthesia, and in four healthy, awake volunteers. All anesthetized patients were deliberately cooled and became hypothermic. Vasoconstriction occurred in five of six at central temperatures between 35.3 and 32.4°C, at end-tidal isoflurane concentrations between 0.74 and 1.65%. The patient who did not vasoconstrict received the highest isoflurane concentration (≈2.5%) and reached a central temperature of 31°C. Unanesthetized volunteers also were exposed to cold and each vasoconstricted at a temperature near 37°C. The threshold for thermoregulatory cutaneous vasoconstriction was inversely correlated with anesthetic dose, the thermoregulatory threshold decreasing ≈3°C C%/isoflurane concentration. There were no statistically significant differences between maximum skin-surface temperature gradients in awake volunteers and patients given isoflurane, or between any of the groups when patients from previous studies given halothane or nitrous oxide/fentanyl anesthesia were included in the comparison. These data indicate that the intensity of vasoconstriction, once triggered, is similar during several different types of anesthesia. A high correlation between calf–toe and forearm–fingertip temperature gradients, and between esophageal and tympanic membrane temperatures, also was demonstrated. (Key words: Anesthetics, volatile: isoflurane. Brain: hypotherm. Hypothermia. Temperature, measurement: esophageal; skin; tympanic membrane. Temperature, regulation: setpoint; threshold. Skin: blood flow.)

THERMOREGULATORY peripheral vasoconstriction occurs at a central temperature of 34.4 ± 0.2°C (mean ± SD) during halothane/oxygen and 34.2 ± 0.5°C during nitrous oxide/fentanyl anesthesia. These studies tested only a single-dose regimen of each anesthetic: halothane 0.86 ± 0.05% in oxygen, and 70% nitrous oxide in oxygen and fentanyl administered as a 10 µg/kg loading dose followed by a 4 µg · kg⁻¹ · h⁻¹ infusion. However, anesthetic-induced inhibition of physiologic responses (e.g., circulatory and respiratory) is usually dose dependent. We therefore determined the relationship between anesthetic concentration and the threshold for thermoregulatory vasoconstriction during isoflurane anesthesia.

Thermoregulatory vasoconstriction is characterized by both threshold (central temperature at which vasoconstriction occurs) and intensity. Our previous studies suggested that although the threshold temperature was markedly lowered during anesthesia, vasoconstriction intensity, measured as maximum skin-temperature gradients, was well preserved. To test the hypothesis that intensity of vasoconstriction, once triggered, was well preserved during isoflurane anesthesia, we compared maximum gradients in patients given isoflurane with those determined previously during halothane/oxygen, nitrous oxide/fentanyl anesthesia, and in unanesthetized volunteers.

Peripheral vasoconstriction can be determined using several techniques, including plasymography, xenon washout, iontophoresis, laser Doppler flowmetry, and skin-surface temperature gradients. Among these methods, only skin-temperature gradients (forearm–fingertip skin temperature) are noninvasive, easy to use, inexpensive, and resistant to movement artifact. However, skin-temperature gradients require measurements on an arm without an iv or arterial catheter, and without a blood pressure cuff (each of which may affect peripheral blood flow). Anesthetic and surgical considerations (e.g., an iv infusion in one arm and surgery involving the other) may make reliable arm gradient determination impossible in some patients. We therefore tested the hypothesis that skin-surface temperature gradients measured on a leg (midcalf–toe skin temperature) correlate well with arm gradients.

Materials and Methods

With approval from the University of California Committee on Human Research, and written, informed consent, we studied six ASA Physical Status 1 patients electively donating a kidney to a relative. None was obese, taking medication, or had a history of thyroid disease, dysautonomia, Raynaud’s syndrome, or malignant hyperthermia. Without any preanesthetic medication, anesthesia was induced by inhalation of isoflurane 3–4%, nitrous oxide 70%, and oxygen; thiopental and opioids were not administered. Vecuronium (0.1 mg/kg) was admin-
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istered intravenously, and the trachea of each patient intubated. Anesthesia was maintained during surgery with isoflurane in 30% oxygen and air using a nonrebreathing system. Mechanical ventilation was adjusted to maintain end-tidal $\text{PCO}_2$ at 35 mmHg. Each patient was placed in the lateral decubitus position.

Patients were randomly assigned to receive either the highest isoflurane concentration compatible with systolic blood pressure between 110 and 120 mmHg or the lowest concentration compatible with diastolic blood pressure between 85 and 90 mmHg. End-tidal isoflurane concentrations were determined using a mass spectrometer (Medspect®, St. Louis, Missouri). Hypothermia was induced by administering 4–7 l iv lactated Ringer's solution cooled to 4°C, keeping the room cool (≈21°C), and avoiding warming blankets and airway humidification.

Tympanic, esophageal, skin, and room temperatures were measured using Mon-a-Therm® model 7000 thermometers and disposable thermocouples (St. Louis, Missouri). The esophageal probe was incorporated into an esophageal stethoscope and positioned at the distal end of the range of maximal heart sounds. (Esophageal temperatures were unavailable in one of six patients.) The tympanic thermocouples were cotton-covered, flexible probes placed in contact with the tympanic membrane. Skin temperatures were measured using thermocouples incorporated into self-sticking, 1-cm-diameter disks at the following sites: midway between wrist and elbow on the radial aspect of the forearm, tip of index finger, front of midcalf, and tip of big toe.

Peripheral vasoconstriction was quantified using skin-surface temperature gradients (forearm–fingertip) on the nondependent arm, which was kept exposed to room air. This indirect measure of peripheral blood flow correlates well with laser Doppler flowmetry and volume plethysmography. The iv catheter was inserted in a vein and the blood pressure cuff placed on the opposite arm. As in our previous studies, significant vasoconstriction was prospectively defined as a forearm–fingertip skin-temperature gradient ≥ 4°C. The thermoregulatory threshold for vasoconstriction was defined as the tympanic membrane temperature at which the forearm–fingertip skin-temperature gradient first exceeded 4°C. An analogous gradient between the midcalf and the big toe was measured on the nondependent leg; these thermocouple sites also were uncovered by drapes. One hour after vasoconstriction, patients were rewarmed using all appropriate techniques.

We also determined the threshold for vasoconstriction and maximum temperature gradients obtained in four unanesthetized, minimally clothed volunteers by exposing them to ambient temperatures similar to those of the kidney donors. These subjects received no additional cooling with cold iv fluids. Measurement techniques were similar to those used in the patients. After significant vasoconstriction occurred in the fingers, we observed stability of the gradient for 60 min. All studies were conducted between 8 A.M. and 6 P.M.

We analyzed the following relationships using least-squares regression and Pearson product-moment correlation: end-tidal isoflurane concentration versus threshold temperature; esophageal versus tympanic temperatures; and forearm–fingertip versus leg–toe skin-temperature gradients. Maximum gradients for awake volunteers, patients given isoflurane, and patients in our previous studies given halothane, or nitrous oxide/fentanyl anesthesia were analyzed using ANOVA and Student-Newman-Keuls test for multiple comparisons. Demographic data in the awake and anesthetized subjects were compared using unpaired, two-tailed t tests. Data are expressed as mean ± standard deviation; $P < 0.05$ identified statistically significant differences.

Results

Significant vasoconstriction occurred in the fingers of all the cold-exposed volunteers at central temperatures between 36.8 and 37.6°C. The six isoflurane-anesthetized patients became hypothermic, and significant vasoconstriction (skin-temperature gradient ≥ 4°C) developed in five of them at central temperatures between 35.3 and 32.4°C, at end-tidal isoflurane concentrations from 0.74 to 1.65%. The single patient in whom vasoconstriction did not occur, had the highest end-tidal isoflurane concentration (2.5%) and became most hypothermic (31°C).

Figure 1 shows that end-tidal isoflurane concentration and thermoregulatory threshold were inversely proportional, related by the regression equation: Threshold (°C) = 37.1 − 3.1 · isoflurane; $r = -0.97$ ($P < 0.001$). For comparison, the threshold during halothane/oxygen anesthesia at ≈1.2 MAC$^<$ (34.2 ± 0.2°C; n = 5) also appears in this figure. The halothane threshold is significantly higher than that calculated from the regression for 1.2 MAC isoflurane (32.8 ± 0.5°C).

Once vasoconstriction started, the arm gradients increased to more than 4°C with little further change in central temperature (fig. 2). The interval between induction of anesthesia and significant vasoconstriction (arm gradient ≥ 4°C) was longer in patients with higher end-tidal isoflurane concentrations (fig. 3).
FIG. 1. The thermoregulatory threshold is inversely correlated with end-tidal isoflurane concentration. The line indicates the least-squares regression calculated from the nine subjects in whom vasoconstriction occurred: Threshold (°C) = 37.1 - 3.1 \cdot [\text{isoflurane}], r = -0.97. The thermoregulatory threshold during halothane anesthesia, obtained during a previous study,\textsuperscript{1} is also indicated. Percent isoflurane is shown on the lower X axis; MAC for isoflurane and halothane is shown on the upper X axis. The individual in whom vasoconstruction did not occur is indicated by the open square (\textcircled{C}). This individual had the highest end-tidal isoflurane concentration (2.5\%) and become most hypothermic (31° C).

Maximum arm skin-surface temperature gradients in the patients who vasoconstricted were 7.8 ± 1.0°C in those given isoflurane (n = 5); 6.9 ± 0.8°C in those given halothane (n = 5);\textsuperscript{1} 6.1 ± 1.1°C in those given nitrous oxide/fentanyl (n = 6);\textsuperscript{2} and 8.1 ± 1.8°C in the unanesthetized volunteers (n = 4). The maximum gradients did not differ significantly in these four groups, although there was a trend towards higher gradients in the unanesthetized volunteers.

Arm and leg temperature gradients typically increased and decreased simultaneously, leg gradients usually being slightly greater than arm gradients (fig. 4). The correlation between arm and leg gradients is shown in fig. 5: Gra-

FIG. 2. Skin-surface temperature gradient versus tympanic membrane temperature at different end-tidal isoflurane concentrations in three patients (isoflurane concentrations 0.95\%, 1.17\%, and 1.3\%) and one volunteer (no isoflurane, 0.0\%). As vasoconstruction is triggered the temperature gradient increases abruptly with only minimal further changes in central temperature. An arrow indicates direction of time. Constriction patterns in the remaining subjects were similar but are omitted for clarity.

FIG. 3. A plot of arm gradients versus time in four patients demonstrates a similar pattern of thermoregulatory vasoconstriction regardless of anesthetic concentration. However, time from induction to vasoconstruction increases with anesthetic concentration because cooling to the lower temperatures (needed to trigger vasoconstruction at higher concentrations) requires extra time.

FIG. 4. Changes in arm gradient (forearm–fingertip) and leg gradient (calf–toe) in one anesthetized patient (the one omitted from fig. 3). Variation in the gradients before significant vasoconstruction are considerably greater than normal, but the simultaneous changes are typical.
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FIG. 5. A good correlation between calf-toe gradient and the previously validated forearm-fingertip gradient was obtained, yielding the regression equation: \( \text{Gradient}_{\text{reg}} (\degree C) = 1.2 \cdot \text{Gradient}_{\text{arm}} + 0.74, r = 0.94. \)

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Tympanic membrane and distal esophageal temperatures were similar (fig. 6). Tympanic (\( \degree C \)) = 0.95. Esophageal + 1.56, \( r = 0.99. \)

Patients given isoflurane and unanesthetized volunteers did not differ significantly in age (40 ± 14 vs. 31 ± 7 yr) or height (166 ± 11 vs. 170 ± 6 cm). The patients weighed significantly more than the volunteers (72 ± 10 vs. 59 ± 4 kg), all with a body mass index below 29 (BMI = weight [kg]/[height (m)]²). There were five women in the isoflurane group and two among the awake volunteers. Ambient temperatures were similar for both groups, ranging from 19.5 to 21.6\( \degree \)C.

Discussion

Our data indicate that isoflurane produces a dose-dependent lowering of the threshold for thermoregulatory vasoconstriction, that the dose-response curve is approximately linear up to 1.5 MAC, and that its slope is steep (\( \approx 3\% \text{ MAC} \left/ \% \text{ isoflurane} \right. \)).

Cold-induced vasoconstriction is generally centrally mediated (finger blood flow is minimally affected at local temperatures between 15 and 35\( \degree \)C). When vasoconstriction occurred, the gradient relatively quickly reversed from a stable temperature near \(-1\degree \)C, to \(\geq 4\degree \)C (fig. 3). This pattern was observed in both anesthetized and awake subjects. The gradual increase expected if passive local cooling were the cause was not observed.

In vitro experiments indicate that most anesthetics produce a direct, dose-related relaxation of vascular smooth muscle in both arteries and veins, the latter being more sensitive to this depressant effect. In vivo, isoflurane increases cutaneous and striated muscle blood flow more than most other inhaled anesthetics. The isoflurane-induced vasodilation is dose-dependent, whereas dilation produced by halothane is not. Isoflurane-induced vasodilation appears to be mediated by \( \beta \)-adrenergic stimulation of vascular smooth muscle. Because \( \beta \) receptors are not believed to play a role in thermoregulatory vasoconstriction, the increased blood flow through arteriovenous anastomoses in fingers and toes following induction of isoflurane anesthesia is most likely due to interference with central thermoregulatory mechanisms. Although isoflurane, halothane, and nitrous oxide/fentanyl anesthesia significantly decreased the thermoregulatory threshold temperatures (a central function), the maximum gradients that developed with each anesthetic were similar to those in awake volunteers. Therefore, the centrally mediated peripheral response, once triggered, appeared well preserved during anesthesia, overriding direct vascular effects of the anesthetic agents.

Dose-dependent hypothermia occurs in animals following systemic administration of sedatives, and ethanol. Despite pronounced central effects, a drug's principal thermal influence may be peripheral. For example, direct peripheral effects of phenothiazines (increased heat loss) and barbiturates (decreased heat production) are believed to dominate their central thermoregulatory effects. Whether inhibition of vasoconstriction is central or peripheral cannot be established with certainty by systemic drug administration, as in this study. However, the pattern of vasoconstriction (relatively little change, followed by rapid development of a large gradient) suggests central mediation.

In our previous studies with halothane, and nitrous

FIG. 6. The correlation between distal esophageal and tympanic membrane temperatures in five patients electively donating a kidney. The regression equation is: Tympanic (\( \degree C \)) = 0.95 \cdot \text{Esophageal} + 1.56, \( r = 0.99. \) indicating that a thermometer carefully placed in the distal esophagus is a valid measure of central body temperature in adults not given airway humidification.
oxide/fentanyl,\textsuperscript{2} patients vasoconstricted \(\approx 100\text{–}190\) min after anesthesia induction. In hypothermic dogs a delay of the same magnitude has been observed between administration of a single dose of chloralose-urethane and the appearance of thermoregulatory responses. Partial restoration of the initially inhibited thermoregulatory functions was assumed to have occurred in the interim.\textsuperscript{20} Similarly, it has been suggested that the appearance of vasoconstriction in our previous patients was due to a time-dependent restoration of thermoregulatory capability.\textsuperscript{21} Such restoration during constant and continuous delivery of an anesthetic seems unlikely. Instead, increasing hypothermia is the factor most likely evoking thermoregulatory responses. In contrast, a single dose of chloralose-urethane would be partially metabolized after 2–3 h, decreasing anesthetic depth and central depression throughout the study period, thus permitting thermoregulatory responses after some time.

The interval between induction of anesthesia and vasoconstriction was relatively constant in our previous studies because the thresholds and cooling rates were similar. However, in the present study, vasoconstriction occurred as early as 50 min following induction (lowest concentration and highest threshold temperature) and as late as 280 min (highest concentration and lowest temperature). Patients given higher doses of isoflurane had lower thermoregulatory thresholds and therefore required longer time to become sufficiently hypothermic to trigger vasoconstriction.

During anesthesia, a gradient of \(\approx 4^\circ\) C in the leg (lower leg–big toe temperature) occurred 10–50 min before a gradient of the same magnitude in the arm (forearm–fingertip), and corresponded to a leg gradient \(\approx 6^\circ\) C. These data suggest that, for anatomic or physiologic reasons, gradients in the toes develop more readily than those in the fingers.

We measured central temperatures in the lower quarter of the esophagus in our previous studies. Despite considerable evidence that distal esophageal temperatures are accurate in general surgical patients\textsuperscript{22} and those undergoing cardiopulmonary bypass,\textsuperscript{23} the validity of esophageal temperatures in our patients has been questioned.\textsuperscript{24} We therefore measured both tympanic membrane and esophageal temperatures in this study. Not surprisingly, the correlation between the two measures was excellent (\(r = 0.99\); fig. 6).

Hypothermia decreases MAC \(\approx 5\%/\circ\) C.\textsuperscript{25,26} However, the relatively modest increase in anesthetic potency resulting from moderate hypothermia in our patients is insufficient to explain the substantial inhibition of thermoregulatory vasoconstriction observed. Mean weight of the kidney donors was \(\approx 13\) kg higher than that of the unanesthetized volunteers. This small difference in body mass is unlikely to have an important thermoregulatory influence.\textsuperscript{27,28}\n
Previously we observed that central temperatures remained constant after vasoconstriction.\textsuperscript{1} Thermal steady state occurs when environmental heat loss equals metabolic heat production. It is, therefore, likely that thermoregulatory responses decrease heat loss (vasoconstriction) and/or increase heat production (nonshivering thermogenesis) sufficiently to produce a thermal steady state. The results of our present study are similar, although in some patients we were able to decrease central temperatures slightly after vasoconstriction by continued administration of refrigerated iv fluids.

Each patient received a different anesthetic concentration (0.7–2.5\%) for the same type of surgery, and the volunteers received no anesthesia and no surgery. Because it is impossible to vary anesthetic depth over this range independently of surgical stress, it is probable that stress-induced autonomic responses contributed to vasoconstriction in some patients. The patients' lungs were ventilated with dry, cool gases, which may have stimulated cold receptors in the airways, and deep-body thermosensors also may have been stimulated by surgical incision.\textsuperscript{25} Lower central temperatures may have been required to trigger vasoconstriction without contribution from these thermoreceptors.

Interpretation of previous studies has been complicated by patients who reached a passive thermal steady state without becoming sufficiently hypothermic to trigger vasoconstriction.\textsuperscript{2} To avoid this problem we deliberately induced hypothermia in these patients. The risks of mild-to-moderate intraoperative hypothermia do not include impaired coagulation, respiratory depression (in adults), or increased duration of recovery.\textsuperscript{29,30} In contrast, there is considerable evidence that mild hypothermia offers significant protection against ischemia and hypoxia.\textsuperscript{31–35} The complication most commonly attributed to intraoperative hypothermia is shivering-like tremor in the postoperative period, imposing increased cardiorespiratory demands.\textsuperscript{24} However, this tremor can be easily treated (and was, when it occurred in our patients) using iv meperidine\textsuperscript{35} or skin-surface warming.\textsuperscript{36}

The patient given the highest isoflurane concentration (~2.5\%) did not vasoconstrict and thus became more hypothermic than intended. When central temperature approached 31°C, all practical rewarming measures were instituted and within 4 h central temperature exceeded 36°C. Although one might expect all patients to vasoconstrict before central temperatures reach 31°C, extending the regression line in figure 1 to 2.5% isoflurane suggests that the threshold at this concentration is below 30°C. The thermoregulatory effects of higher isoflurane concentrations than those tested in this study remain unknown, and will be difficult to determine because vasoconstriction at higher concentrations will be expected at temperatures usually obtained only during operations involving cardiopulmonary bypass.
In summary, the thermoregulatory threshold for cutaneous vasconstriction in healthy adult humans during isoflurane anesthesia is inversely proportional to anesthetic concentration and decreases $\approx 3^\circ$ C/8% end-tidal isoflurane concentration. The intensity of vasconstriction, once triggered, is well preserved during isoflurane, halothane, and nitrous oxide/fentanyl anesthesia.

The authors wish to thank N. J. Feduska, M.D., J. S. Melzer, M.D., O. Salvaterra, Jr., M.D., and Jane McIntire, R.N. for assistance in studying their patients.

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