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Painful Stimulation Minimally Increases the Thermoregulatory Threshold for Vasoconstriction during Enflurane Anesthesia in Humans

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Generalized autonomic stimulation enhances hemodynamic responses and may, in a similar fashion, facilitate thermoregulatory responses. We thus tested the hypothesis that painful stimulation increases the central temperature threshold for vasoconstriction during general anesthesia. Healthy volunteers were anesthetized with 1.3% end-tidal enflurane on 2 separate days. On 1 day (randomly assigned), painful stimulation was produced by tetanic electrical stimulation. On the other day, electrical stimulation was not given. Significant thermoregulatory vasoconstriction was defined as a forearm − fingertip skin-surface temperature gradient exceeding 4° C. The distal esophageal temperature triggering significant vasoconstriction was considered the thermoregulatory threshold. The threshold was 35.5 ± 0.8° C during electrical stimulation and 35.1 ± 0.6° C without stimulation ($P = 0.050$, 95% confidence interval for the difference = 0–0.7° C). These data suggest that thresholds determined in nonsurgical volunteers will be slightly (but not clinically significantly) less than those in operative patients. Similarly, intraoperative vasoconstriction thresholds likely will be slightly less when surgical pain is prevented by simultaneous regional or local analgesia. (Key words: Anesthetics, volatile: enflurane. Brain: hypothalamus. Hypothermia. Measurement techniques, blood flow: skin-temperature gradient. Temperature, measurement: esophageal; skin. Temperature, regulation: setpoint; threshold; vasoconstriction. Thermoregulation. Vasoconstriction: thermoregulatory.)

SURGICAL STIMULATION produces generalized autonomic stimulation that enhances hemodynamic responses.[1] Noxious stimulation may, in a similar fashion, facilitate thermoregulatory responses by decreasing effective anesthetic level. Thus, at a given anesthetic concentration, facilitation of regulatory responses to hypothermia by surgical pain might produce a higher vasoconstriction threshold in patients than in anesthetized but unstimulated volunteers.

The effect of painful stimulation on thermoregulatory responses is one factor limiting the extent to which results of studies in unstimulated volunteers can be extrapolated to surgical patients. Similarly, if pain is a major factor influencing thermoregulation, response thresholds may differ appreciably between anesthetized patients undergoing stimulating procedures and those in whom surgical pain is prevented by simultaneous regional or local analgesia.

Accordingly, we prospectively tested the hypothesis that painful stimulation increases the central temperature threshold. To permit a randomized, cross-over design (and eliminate confounding factors in surgical patients), we studied anesthetized volunteers with and without electrical stimulation. Because the thermoregulatory threshold for vasoconstriction during enflurane anesthesia remains unknown, we chose this anesthetic for our study.

Materials and Methods

Following approval of the University of California, San Francisco Committee on Human Research, we studied five volunteers (four men and one woman). None was obese or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. None of the men was taking medication, but the woman took oral contraceptives.

During the study, volunteers were minimally clothed and reclined on a standard operating room table. A circulating water mattress was positioned under each volunteer's back (but not in contact with the arms or legs); the mattress was connected to a heating unit set at 42° C (Blanketrol II, Maxi-Therm blanket S276, Cincinnati Sub-Zero, Cincinnati, OH). Ambient temperature was maintained near 25° C. The percentage of body fat in each volunteer was determined using infrared interactance (Futrex 1000, Futrex, Inc., Hagerstown, MD).[2]

Volunteers fasted during the 8 h preceding each study, which started at approximately 10:00 AM. An intravenous catheter was inserted into an antecubital vein on the right arm. Unwarmed lactated Ringer's solution was infused at ≈100 ml/h. Anesthetic-induced redistribution hypothermia[3] was minimized by preinduction skin-surface warming[4] using a forced-air warming device set on "high" (≈43° C) (Bair Hugger® model 200, Augustine Medical, Eden Prairie, MN).[5]

No preanesthetic medication was administered. Anesthesia was induced by inhalation of enflurane 3–5%, nitrous oxide 70%, and oxygen. Vecuronium 10 mg was

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administered intravenously; muscle relaxation was subsequently maintained with an infusion of vecuronium (Program 2 syringe pump, Becton Dickinson & Company, Lincoln Park, NJ) adjusted to maintain zero or one twitch in response to supramaximal train-of-four electrical stimulation of the ulnar nerve at the wrist. Nitrous oxide was discontinued after induction, and the trachea of each patient was intubated.

An Ohmeda Modulus II integrated anesthesia system (Ohmeda, Madison, WI) was used to administer anesthetic gases, to control end-tidal P_{CO_2} to 35 ± 1 mmHg, and to monitor blood pressure, heart rate, and oxygen saturation. Anesthesia was maintained with enflurane in 30% oxygen and 70% nitrogen; the end-tidal enflurane concentration was gradually reduced to 1.3% (0.75 MAC) over ≈30 min, and maintained at that concentration. End-tidal gas concentrations were measured using a mass spectrometer (Medspect®, St. Louis, Missouri). Airway humidification was provided by placing a heat-and-moisture exchanger (ARC Medical, Inc., Clarkston, GA) between the Y-piece of the circle system and the endotracheal tube.

Forced-air warming was discontinued immediately after induction of anesthesia, and the temperature of water circulating in the mattress was decreased to 10° C at a rate of 1° C/min. Throughout anesthesia, we were careful to avoid manipulating the endotracheal tube or causing other unnecessary stimulation.

Each volunteer participated in the study on 2 days separated by at least 72 h; treatment order was assigned randomly. On 1 day, a 15-v, 100-Hz, 65-mA current was passed through needle electrodes inserted into the skin of the abdomen to provide stimulation analogous to surgical pain (Digi Stim III, Neuro Technology, Houston, TX).§ The electrodes were separated by ≈5 cm. Electrical stimulation was started 30 min following induction of anesthesia. Stimulation lasting 5 s was administered twice, at 1-min intervals, at the beginning of each 5-min period. Blood pressure and heart rate were measured just before the first electrical stimulation in each 5-min period (*e.g.*, 4 min after the last stimulation). On the other study day, electrical stimulation was not given.

Central temperature was measured in the distal fourth of the esophagus, and mean skin-surface temperature was calculated from 15 area-weighted sites using disposable thermocouple probes (Mon-a-Therm®, St. Louis, MO). Forearm − fingertip skin-temperature gradients were used to detect peripheral cutaneous vasoconstriction; there is an excellent correlation between skin temperature gradients and absolute finger blood flow.[6] All thermocouples were connected to two calibrated 16-channel electronic thermometers (Iso-Thermex, Columbus Instruments International Corp., Columbus, OH) with an accuracy of 0.1° C and a precision of 0.01° C. Data were recorded at 5-min intervals, using a modification of a previously described data-acquisition system.[7] Each study day concluded when the skin-temperature gradient exceeded 4° C.

As in our previous studies,[8–10] a skin-temperature gradient exceeding 4° C was considered significant vasoconstriction. The central temperature at the time of significant vasoconstriction identified the thermoregulatory threshold. Vasoconstriction thresholds and hemodynamic responses with and without stimulation were compared using two-tailed, paired *t* tests. Differences were considered significant when $P < 0.05$. Results are presented as means ± standard deviations.

Results

The volunteers were 27 ± 2 yr old, weighed 70 ± 16 kg, were 177 ± 9 cm tall, and had 16 ± 5% body fat.

Vasoconstriction occurred 170 ± 37 min following induction of anesthesia when volunteers were stimulated and at 155 ± 37 min without stimulation. The central-temperature threshold triggering peripheral thermoregulatory vasoconstriction was 35.5 ± 0.8° C during electrical stimulation and 35.1 ± 0.6° C without stimulation ($P = 0.050$, 95% confidence interval for the difference = 0–0.7° C) (fig. 1).

Mean skin-surface temperatures, end-tidal carbon dioxide concentration, end-tidal enflurane concentration, and ambient temperature at the time of significant vasoconstriction did not differ significantly with and without electrical stimulation. Arterial blood pressure and heart rate typically increased ≈20% during stimulation and remained elevated for ≈2 min. However, the differences

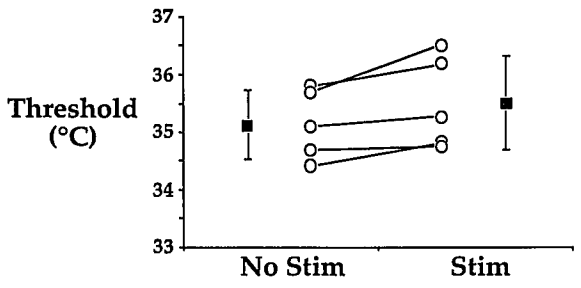

FIG. 1. The central-temperature threshold triggering peripheral thermoregulatory vasoconstriction was 35.5 ± 0.8° C during electrical stimulation ("Stim") and 35.1 ± 0.6° C without stimulation ("No Stim") ($P = 0.050$). The thresholds were not statistically significantly different and the absolute divergence was small.

§ From subsequent consultation with a biomedical engineer, we learned that similar stimulation can be provided with greater safety using silver/silver chloride pads positioned >10 cm apart on well-prepared skin.

TABLE 1. Environmental and Anesthetic Data

	No Stimulation	Stimulation
Mean skin temperature (° C)	29.0 ± 1.1	29.7 ± 0.9
End-tidal CO_2 (mmHg)	35 ± 1	36 ± 1
End-tidal enflurane (%)	1.31 ± 0.02	1.33 ± 0.02
Ambient temperature (° C)	24.6 ± 0.5	24.9 ± 0.5
Systolic blood pressure (mmHg)	102 ± 12	111 ± 17
Heart rate (beats/min)	57 ± 6	66 ± 15

Mean skin-surface temperatures, end-tidal CO_2 concentration, end-tidal enflurane concentration, ambient temperature, systolic arterial blood pressure, and herat rate at the time of significant vasoconstriction did not differ significantly with and without electrical stimulation.

were not statistically significant when we recorded hemodynamic values 4 min after stimulation ($P = 0.1$) (table 1).

Discussion

The difference in thresholds when the volunteers were or were not stimulated was not quite statistically significantly different ($P = 0.050$). However, the absolute divergence was small (0.4° C), as was the 95% confidence interval for the difference (0–0.7° C). Thus, noxious electrical stimulation appears to produce little clinically important increase in the threshold for vasoconstriction during enflurane anesthesia.

Our results are consistent with retrospective data showing that isoflurane-induced inhibition of thermoregulatory vasoconstriction in surgical patients is similar to that in volunteers.[11,12] These data suggest that thresholds determined in nonsurgical volunteers[13,14] will be slightly (but not clinically significantly) less than those in operative patients. Similarly, vasoconstriction thresholds during general anesthesia likely will be slightly less when surgical pain is prevented by simultaneous regional or local analgesia. However, operations producing especially great autonomic stimulation may have larger thermoregulatory effects.

Although hypothalamic control dominates thermoregulatory responses, temperature of the hypothalamus *per se* probably is no more important than that of other tissues including the spinal cord, abdomen, and thorax.[15–17] Surgical patients differ from volunteers not only because the degree of painful stimulation differs, but also because surgical incisions expose thermal receptors in deep tissues that usually are protected from the environment. The extent to which thermal receptors within incisions contribute to thermoregulatory responses remains unknown. However, similar vasoconstriction thresholds in patients undergoing donor nephrectomy[11] and (unstimulated) volunteers[12] during isoflurane anesthesia suggest that the effect is not large. A limited thermoregulatory response to stimulation of local receptors also is consistent with our previous observation that cooling of spinal cord temperature receptors by epidural injection of iced saline[18] or lidocaine[19] does not trigger shivering in humans.

Another difference between volunteers and surgical patients is that hypovolemia is more common during surgery because blood loss can be difficult to estimate accurately. Our clinical studies[8–10] have evaluated patients undergoing procedures causing little blood loss, and we have taken care to maintain adequate vascular volume because volume depletion markedly aggravates thermoregulatory vasoconstriction.[20] However, vasoconstriction thresholds likely will be higher in surgical patients than in volunteers if appropriate intraoperative hydration is not maintained. It also is likely that sufficient vascular volume depletion will produce nonthermoregulatory vasoconstriction.

The vasoconstriction threshold during 0.75 MAC enflurane anesthesia with painful electrical stimulation was 35.5 ± 0.8° C. The dose–response curve for inhibition of thermoregulatory vasoconstriction by halothane remains unknown; however, the vasoconstriction threshold in adult surgical patients given 1.15 MAC is 34.4 ± 0.2° C.[8] If inhibition is a linear function of anesthetic concentration, this would correspond to a threshold of 35.4° C during 0.75 MAC halothane and suggest that halothane and enflurane produce similar thermoregulatory inhibition. The assumption that thermoregulatory inhibition is linear with anesthetic dose is reasonable since that is the case during isoflurane anesthesia.[11] However, 0.75 MAC of isoflurane in adult surgical patients reduces the vasoconstriction threshold to ≈34.5° C, suggesting that isoflurane causes more thermoregulatory inhibition than do halothane and enflurane. This conclusion is supported by the observation in infants and children that vasoconstriction thresholds are consistently higher during 0.8–1.2 MAC halothane (≈35.8° C)[21] than during 0.8 MAC isoflurane (≈34.8° C).[10]

It remains possible that thermoregulatory responses other than vasoconstriction (*e.g.*, shivering) are altered to a greater degree by painful stimulation. However, retrospective data suggest that sweating thresholds, at least, are similar in surgical patients and unstimulated volunteers.[22,23] It is likely that the thermoregulatory effects of pain do differ among anesthetics: the effect of stimulation may be less with anesthetics providing good analgesia (*e.g.*, opioid-based drugs) or greater with those that do not (*e.g.*, neuroleptic drugs). Finally, the thermoregulatory effects of painful stimulation may be enhanced at low anesthetic concentrations that cause generalized central nervous system excitement (manifested by hyperalgesia,[24] enhanced learning,[25] and abnormal spinal cord reflexes[26–29]).

Tetanic electrical stimulation at 15 v in rats produces a supramaximal pain similar to that produced by surgical

incisions¶; similar stimulation has been used in studies of volatile anesthetic requirement and hemodynamic responses to pain in humans.[30] Electrical current as applied in this study likely provided autonomic stimulation similar to that produced by many surgical procedures. However, the amount of autonomic activation produced by various surgical procedures clearly differs; electrical stimulation almost surely produces less autonomic activation than the largest operations. Although our cross-over study design did not include autonomic activation comparable to that produced by very extensive surgery, it did permit direct comparison of the thresholds in each volunteer with, and without, stimulation sufficiently painful that it would be unbearable without anesthesia.

The autonomic responses to electrical stimulation (increased heart rate, blood pressure, and pupil size) require 2–4 min to return to baseline values.[31] Although the blood pressure and heart rate were not statistically significantly different on the 2 treatment days ($P = 0.1$), both were higher when the volunteers were stimulated. Hemodynamic differences would have been exaggerated (and highly statistically significant) had measurements been recorded during or immediately after electrical stimulation.

Our choice of anesthetic concentration was based on maintaining a suitable blood pressure (when the volunteers were not stimulated) and not excessively reducing the vasoconstriction threshold (which would significantly increase the required duration of anesthesia). Systolic blood pressure averaged only 100 mmHg when the volunteers were unstimulated, and it is thus unlikely that they could have tolerated much more anesthesia. Noxious stimulation may alter thermoregulatory thresholds differently at other anesthetic concentrations. However, the difference is likely to be greater at *lower* anesthetic concentrations when pain is better perceived; it thus seems unlikely that the difference will be exaggerated at higher (*e.g.*, surgical) concentrations of enflurane.

In summary, the thermoregulatory threshold for vasoconstriction during 0.75 MAC enflurane was 35.5 ± 0.8° C with painful electrical stimulation and 35.1 ± 0.6° C without stimulation ($P = 0.050$). The absolute divergence was small (95% confidence interval for the difference = 0–0.7° C) and probably of little clinical importance. These data suggest that thresholds determined in nonsurgical volunteers will be slightly less than those in operative patients. Similarly, vasoconstriction thresholds during general anesthesia likely will be slightly less when surgical pain is prevented by simultaneous regional or local analgesia.

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