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Thermoregulatory Thresholds for Vasoconstriction in Patients Anesthetized with Various 1-Minimum Alveolar Concentration Combinations of Xenon, Nitrous Oxide, and Isoflurane

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Background: **Nitrous oxide limits intraoperative hypothermia because the vasoconstriction threshold with nitrous oxide is higher than with equi–minimum alveolar concentrations of sevoflurane or isoflurane, presumably because of its stimulating actions on the sympathetic nervous system. Xenon, in contrast, does not cause sympathetic activation. Therefore, the authors tested the hypothesis that the vasoconstriction threshold during xenon–isoflurane anesthesia is less than during nitrous oxide–isoflurane anesthesia or isoflurane alone.**

Methods: **Fifteen patients each were randomly assigned to one of three 1-minimum alveolar concentration anesthetic regimens: (1) xenon, 43% (0.6 minimum alveolar concentration) and isoflurane, 0.5% (0.4 minimum alveolar concentration); (2) nitrous oxide, 63% (0.6 minimum alveolar concentration) and isoflurane 0.5%; or (3) isoflurane, 1.2%. Ambient temperature was maintained near 23°C and the patients were not actively warmed. Thermoregulatory vasoconstriction was evaluated using forearm-minus-fingertip skin temperature gradients. A gradient exceeding 0°C indicated significant vasoconstriction. The core-temperature threshold that would have been observed if skin had been maintained at 33°C was calculated from mean skin and distal esophageal temperatures at the time of vasoconstriction.**

Results: **The patients' demographic variables, preinduction core temperatures, ambient operating room temperatures, and fluid balance were comparable among the three groups. Heart rates were significantly less during xenon anesthesia than with nitrous oxide. The calculated vasoconstriction threshold was lowest with xenon (34.6 ± 0.8°C, mean ± SD), intermediate with isoflurane alone (35.1 ± 0.6°C), and highest with nitrous oxide (35.7 ± 0.6°C). Each of the thresholds differed significantly.**

Conclusions: **Xenon inhibits thermoregulatory control more than isoflurane, whereas nitrous oxide is the least effective in this respect. (Key words: Anesthesia; heat; temperature; thermoregulation.)**

XENON has recently attracted renewed interest because it possesses many characteristics of an ideal anesthetic. For example, (1) the minimum alveolar concentration (MAC) of xenon is 71%, so xenon alone can provide anesthesia for surgery under normobaric conditions[1]; (2) xenon is analgesic, with a potency similar to that of nitrous oxide[2,3]; (3) the toxicity of xenon is low,[4] because it is chemically inert and probably does not un-

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dergo biotransformation; (4) xenon produces minimal hemodynamic depression[5,6]; and (5) xenon is environmentally friendly, because it is prepared by fractional distillation of air.[4]

A prominent feature of xenon is its blood–gas partition coefficient of only 0.12 to 0.14,[7,8] which is smaller than that of nitrous oxide. Therefore, xenon provides faster emergence from anesthesia than other inhalational agents,[9] and emergence times are not prolonged even after long periods of anesthesia.[10] The primary disadvantage of xenon is that the gas is expensive. Fortunately, the xenon requirements per hour of anesthesia decrease progressively during closed-circuit anesthesia.[10] This makes xenon an economically viable anesthetic choice for long operations.

Inadvertent hypothermia often complicates prolonged surgery. In patients becoming sufficiently hypothermic, reemergence of thermoregulatory vasoconstriction usually prevents further core hypothermia.[11] Nitrous oxide may, to some extent, restrict intraoperative hypothermia, because its vasoconstriction threshold is higher than equi-MACs of sevoflurane or isoflurane.[12] The relatively high vasoconstriction threshold during nitrous oxide anesthesia is presumably related to the drug's sympathetic nervous system activation.[13–15] Xenon, in contrast, does not cause sympathetic activation[5,16] and attenuates the hemodynamic response to skin incision more effectively than isoflurane or sevoflurane.[17]

Therefore, we tested the hypothesis that the vasoconstriction threshold during xenon–isoflurane anesthesia is less than during isoflurane alone. We took this opportunity to simultaneously confirm our previous observation that the threshold is higher during nitrous oxide–isoflurane anesthesia than when isoflurane is used alone.

Methods

With institutional review board approval and written informed patient consent, we studied 45 patients classified as American Society of Anesthesiologists physical status 1 and 2. All were aged 32 to 65 yr and were undergoing elective abdominal surgery. Potential participants were excluded if they had a history of thyroid disease, dysautonomia, Raynaud's syndrome, malignant hyperthermia, or cerebrovascular or other central nervous system diseases.

Protocol

No premedication was administered. When they arrived in the operating suite, all patients were given 10 ml/kg unwarmed intravenous fluid. General anesthesia was induced by intravenous administration of 2 mg/kg propofol, and the lungs were ventilated with oxygen containing progressively increasing concentrations of isoflurane. The patients' tracheas were intubated after muscle relaxation was induced by administration of 0.1 mg/kg vecuronium bromide.

Fifteen patients each were assigned randomly to one of three, 1-MAC anesthetic regimens: (1) xenon, 43% (0.6 MAC) and isoflurane, 0.5% (0.4 MAC); (2) nitrous oxide, 63% (0.6 MAC), and isoflurane, 0.5%; or (3) isoflurane, 1.2%.[1,18] We assumed the additivity of xenon and isoflurane MAC fractions because those of xenon and halothane are known to be additive.[1] These maintenance anesthetics were delivered *via* a closed-circuit breathing system to limit the expenditure of xenon. During the period between skin incision and the application of peritoneal retractors, however, the concentration of isoflurane was increased temporarily if mean arterial pressure exceeded the preinduction value by more than 30%. No additional anesthetics, sedative, or opioids were given subsequently until the end of surgery.

Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure between 32 and 35 mmHg. Supplemental vecuronium was administered as needed to maintain zero-to-two twitches in response to supramaximal stimulation of the ulnar nerve at the wrist. At least 8 $ml \cdot kg^{-1} \cdot h^{-1}$ unwarmed intravenous fluid was administered during the study period to maintain urine output of at least 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$.

An antimicrobial airway filter (Hygrobac S-M; Mallinckrodt Medical, St. Louis, MO) was used for passive humidification from the outset of mask ventilation, and the patients were covered with a single layer of surgical draping. No other warming measures were used during the study. Ambient temperature was maintained near 22–23°C.

Once significant vasoconstriction was observed (explained subsequently), patients were actively rewarmed using appropriate measures, including forced air and circulating water. Subsequent anesthetic management was left to the discretion of the responsible anesthetist. If vasoconstriction had not occurred within 1.5 h of the anticipated completion of surgery, active rewarming was started; data from these patients were excluded from analysis. All the patients had a core temperature of more than 35.8°C by the end of anesthesia and more than 36.5°C before they were discharged from the postanesthesia care unit.

Measurements

Core temperature was measured at the tympanic membrane before anesthesia was induced and from the distal esophagus thereafter. 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 taped in place, the aural canal occluded with cotton, and the external ear covered with a gauze pad.

Mean skin temperature was calculated from four sites (the anterior chest, upper arm, thigh, and calf) using the formula: $T_{skin} = 0.3(T_{chest} + T_{arm}) + 0.2(T_{thigh} + T_{calf})$.[19] All temperatures were measured using Mon-a-Therm model 6510 thermometers and disposable thermocouples (Mallinckrodt Medical, St. Louis, MO). Ambient temperature was measured using a thermocouple positioned at the level of the patient, well away from any heat-producing equipment.

Thermoregulatory vasoconstriction was evaluated using forearm-minus-fingertip skin temperature gradients.[20] Skin temperature gradients were recorded from an arm exposed to the operating room environment that was not encumbered by a blood pressure cuff or intravascular catheter. 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.

Blood pressure was determined oscillometrically or from an arterial catheter when one was inserted for clinical purposes. Heart rate was monitored continuously using a three-lead electrocardiograph. The end-tidal concentrations of nitrous oxide, carbon dioxide, and isoflurane were measured using an infrared analyzer (PM8050 anesthesia monitor, Drägerwerk, Lübeck, Germany); end-tidal xenon concentrations were monitored using an AZ-720 analyzer (Anzai Medical, Tokyo, Japan), which has a working range of 1–100% with the error ±1% and the 90% response time less than 1 s. The gases sampled by these monitors were returned to the breathing circuit after analysis.

Data Analyses

As in previous studies,[12] we considered a gradient exceeding 0°C (*i.e.*, fingertip colder than forearm) as indicative of significant thermoregulatory vasoconstriction. The cutaneous contribution to vasoconstriction is linear.[21] Thus, we used measured skin and core temperatures at the time of vasoconstriction to calculate the core-temperature threshold that would have been observed had skin been maintained at a single designated temperature:

$$T_{Core(calculated)} = T_{Core} + \left(\frac{\beta}{1-\beta}\right)[T_{Skin} - T_{Skin(designated)}] \quad (1)$$

where the fractional contribution of the mean skin temperature to the threshold was termed B. $T_{Core(calculated)}$ thus equals the measured core temperature, T_{Core}, plus a small correction factor consisting of B/(1 − B) multiplied by the difference between actual (T_{skin}) and designated ($T_{skin[designated]}$) skin temperatures. We have previously described the derivation, validation, and limitations of this method.[22] We used a B of 0.2 for vasoconstriction,[21] and the designated skin temperature was set at 33°C, a typical intraoperative value.

Heart rate, mean arterial blood pressure, anesthetic gas concentrations, and ambient temperature were first averaged within each patient during the 20 min preceding the onset of significant vasoconstriction, and then among the patients in each treatment group. Results were compared using one-way analysis of variance and Student and Newman–Keuls tests for *post hoc* multiple comparisons. Data are expressed as the mean ± SDs; $P < 0.05$ was considered significant.

Results

Thermoregulatory vasoconstriction was not observed in two patients given xenon, in three patients given nitrous oxide, and in two patients given isoflurane alone. Data analysis was thus restricted to the remaining 13 patients each in the xenon and isoflurane groups and 12 patients in the nitrous oxide group.

The patients' demographics, preinduction core temperatures, ambient operating room temperatures, and fluid balance were comparable among the three groups (table 1). In two patients each from the xenon and nitrous oxide groups, the concentration of isoflurane was increased to 1% for less than 10 min between skin incision and the application of the peritoneal retractor to suppress excessive hemodynamic responses. Otherwise, end-tidal concentrations of xenon, nitrous oxide, and isoflurane were close to target values (table 2).

The mean arterial pressures were similar in the three anesthetic treatment groups, but heart rates were significantly less during xenon anesthesia than with nitrous oxide (table 1). Core cooling rates were similar (table 2). The threshold for vasoconstriction, calculated at a designated mean skin temperature of 33°C, was lowest with

Table 1. Morphometric and Demographic Characteristics, Environmental Data, and Hemodynamic Responses

	Xenon	N_2O	Isoflurane
Age (yr)	54 ± 9	57 ± 9	58 ± 8
Gender (male/female)	9/4	9/3	9/4
Height (cm)	163 ± 8	161 ± 8	163 ± 7
Weight (kg)	61 ± 12	56 ± 10	59 ± 8
Pre-induction core temperature (°C)	37.1 ± 0.2	37.2 ± 0.3	37.0 ± 0.2
Ambient temperature (°C)	23.2 ± 0.6	23.0 ± 1.0	23.2 ± 0.7
Fluid administration ($ml \cdot kg^{-1} \cdot h^{-1}$)	11 ± 3	11 ± 5	10 ± 4
Urinary output ($ml \cdot kg^{-1} \cdot h^{-1}$)	2 ± 1	2 ± 1	2 ± 1
Heart rate (bpm)	65 ± 13*	79 ± 12	72 ± 9
Mean arterial pressure (mmHg)	110 ± 15	106 ± 10	95 ± 22

Values are mean ± SD.

* Significantly different from N_2O.

xenon, intermediate with isoflurane alone, and highest with nitrous oxide. Each of the thresholds differed significantly (fig. 1).

Discussion

Our major finding is that the vasoconstriction threshold was significantly less during xenon–isoflurane anesthesia than during an equi-MAC fraction of isoflurane alone. We have also confirmed our previous observation that the vasoconstriction threshold is greater during nitrous oxide–isoflurane anesthesia than during isoflurane alone.[12] Our protocol does not identify the specific mechanism by which xenon inhibits thermoregulation more than isoflurane or nitrous oxide. However, several possibilities warrant consideration.

Table 2. Core Cooling Rates, Anesthetic Concentrations, Mean Skin and Core Temperatures, and Calculated Thresholds

	Xenon	N_2O	Isoflurane
Core cooling rate (°C/h)	1.0 ± 0.5	1.4 ± 0.8	1.2 ± 0.5
Time to constriction (h)	2.7 ± 0.7*†	1.4 ± 0.6	1.8 ± 0.8
End-tidal isoflurane (%)	0.54 ± 0.05	0.52 ± 0.04	1.2 ± 0.08
End-tidal xenon or N_2O (%)	43 ± 1	63 ± 1	—
Mean skin temperature (°C)	32.0 ± 1.0*†	33.0 ± 0.6	33.1 ± 0.6
Core temperature (°C)	34.8 ± 0.6*	35.7 ± 0.5†	35.1 ± 0.5
Calculated threshold (°C)	34.6 ± 0.8*†	35.7 ± 0.6†	35.1 ± 0.6

Thresholds were calculated at a designated skin temperature of 33°C. Results are reported as mean ± SD.

* Significantly different from N_2O.

† Significantly different from isoflurane.

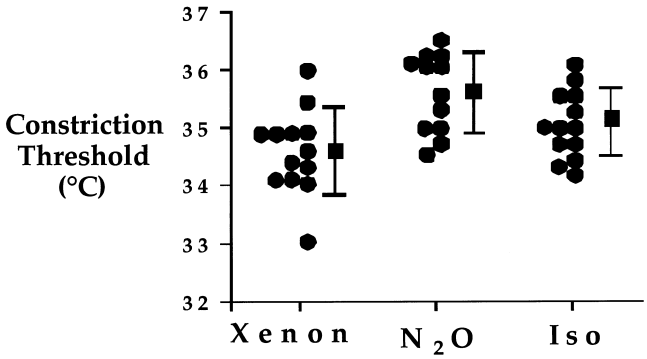

Fig. 1. The vasoconstriction thresholds were 34.6 ± 0.8°C during xenon, 35.7 ± 0.6°C during nitrous oxide (N_2O), and 35.1 ± 0.6°C during isoflurane (Iso) alone. All three thresholds differed significantly.

First, the activity of the sympathetic nervous system may play a role. The anesthetic associated with the highest vasoconstriction threshold in our study was nitrous oxide, a well-established activator of the sympathetic nervous system. Activation has been demonstrated by elevated plasma catecholamine concentrations[13] and more recently by microneurography.[14,15] In contrast, the agent with the lowest vasoconstriction threshold, xenon, decreases plasma catecholamine concentrations,[16] indicating that the drug produces a sympatholytic effect. Furthermore, heart rate (which is one indicator of sympathovagal balance[23]) was significantly reduced during xenon administration in the current study as well as some, although not all, previous investigations.[5,6,17] This parallel relation between the vasoconstriction thresholds of anesthetics and their sympathetic activating properties suggests that the thermoregulatory effects of general anesthetics are modulated by their effects on the sympathetic nervous system.

Second, the potent analgesic effect of xenon[2,3] might have attenuated the effect of painful surgical stimulation to increase the vasoconstriction threshold.[24] In contrast, isoflurane has only limited, if any, analgesic properties,[25] which might have permitted surgical stimulation to elevate the vasoconstriction threshold compared with xenon. However, analgesia alone cannot account for the high vasoconstriction threshold of nitrous oxide, suggesting that another mechanism must also be operative.

The third potential mechanism underlying the observed differences in the vasoconstriction thresholds

may include failure of nitrous oxide to inhibit the hypothalamic thermoregulatory centers as well as isoflurane or xenon did. The effect of nitrous oxide on the cerebral metabolic rate is highly region specific, both in animals[26] and humans.[27] In contrast, the effects of isoflurane are considerably more homogeneous.[28,29] No reports have described regional brain metabolism during xenon anesthesia. However, xenon produces a generalized, rather than regional, increase in cerebral perfusion.[30] This observation suggests that metabolic rate (and anesthetic effect) are likely to be homogeneous during xenon anesthesia, because cerebral blood flow is well correlated with metabolism during inhalation anesthesia.[31] Thus, we can speculate that xenon and isoflurane might "anesthetize" the hypothalamus better than nitrous oxide.

One important concept that can be drawn from our results is that the thermoregulatory effects of anesthetic drugs are not directly related to their anesthetic potency (*i.e.*, MAC), because 1-MAC anesthesias produced by three different anesthetic regimens differ in their ability to prevent thermoregulatory vasoconstriction. Similarly, the vasoconstriction and shivering thresholds during isoflurane[32] and desflurane[33] anesthesia are nonlinear, whereas anesthetic potency is thought to be a direct function of MAC fraction. These discrepancies between MAC and thermoregulatory effects may be accounted for, at least in part, by the difference in the central nervous system structures mediating the two phenomenon: The end point for the determination of MAC (aversive movement to skin incision) is largely mediated spinally,[34] whereas thermoregulation is predominantly a supraspinal phenomenon (*e.g.*, through the hypothalamus).

The vasoconstriction threshold during xenon–isoflurane anesthesia was reduced a full degree centigrade compared with nitrous oxide–isoflurane anesthesia. This difference is likely to be clinically important because major benefits[35] and complications[36,37] of hypothermia have been demonstrated at only slightly greater temperature differences. Furthermore, there is now evidence that differences as small as 0.5°C can influence patient outcome.[38] Most patients require active warming to prevent intraoperative hypothermia.[39] However, vasoconstriction prevents additional hypothermia in patients who become sufficiently cold to activate this thermoregulatory defense.[11] Conversely, vasoconstriction impedes active cooling during therapeutic hypothermia.[11] Under these circumstances, patient temperature is likely to be significantly altered by the choice of either xenon or nitrous oxide anesthesia.

A limitation of our protocol is that we tested only one concentration each of xenon and nitrous oxide. However, we used nitrous oxide, 63%, which is near the maximum that can be administered safely at one atmosphere. The xenon concentration was chosen to provide an equi-MAC fraction. Presumably, xenon and nitrous oxide thresholds would differ less from isoflurane alone had we given lesser concentrations. We only tested the vasoconstriction threshold because shivering is rare during clinical anesthesia. Furthermore, the shivering threshold remains 1°C less than the vasoconstriction threshold with all anesthetics,[32,33] opioids,[40] and sedatives,[22,41] except meperidine.[42]

Another potential limitation is that we gave isoflurane to all groups, which might reduce our ability to distinguish the effects of fractional MAC doses of nitrous oxide and xenon. However, this study was designed to compare the three anesthetics at an equi-MAC fraction (0.6 MAC), with all of them supplemented by additional isoflurane (0.4 MAC) to provide adequate surgical anesthesia. It remains unknown, however, whether the 0.6 MAC concentrations of the three anesthetics interact similarly with 0.4 MAC isoflurane on thermoregulation. Notably, 0.6 MAC and 0.4 MAC doses of isoflurane do not follow simple additivity when their thermoregulatory actions are concerned.[32]

In conclusion, the threshold for vasoconstriction, calculated at a designated mean skin temperature of 33°C, was lowest with xenon (34.6 ± 0.8°C), intermediate with isoflurane alone (35.1 ± 0.6°C), and highest with nitrous oxide (35.7 ± 0.6°C). One likely mechanism underlying these differences is the differential effects of these anesthetics on the sympathetic nervous system activity. Because vasoconstriction is a major physiologic defense against hypothermia but is impaired most profoundly by xenon, clinicians should be especially careful to prevent inadvertent hypothermia during xenon anesthesia.

Xenon was provided by Daido Hoxan, Inc., Tokyo, Japan. Thermometers and thermocouples were provided by Mallinckrodt, Inc., St. Louis, MO.

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