Anesthesiology
81:353–360, 1994

Propofol Causes a Dose-dependent Decrease in the Thermoregulatory Threshold for Vasoconstriction but Has Little Effect on Sweating

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Background: **Volatile anesthetics increase the core temperature required to trigger sweating and decrease the core temperature required to trigger vasoconstriction. However, little is known about the effects of intravenous anesthetics on thermoregulation. We therefore tested the hypothesis that propofol increases the sweating threshold and decreases the vasoconstriction threshold, thereby increasing the interthreshold range (core temperatures *not* triggering autonomic thermoregulatory responses). The study was conducted using a new model in which thermal manipulations were restricted to insensate skin, and sensate skin temperature was controlled.**

Methods: **Six healthy, male volunteers were studied on 3 randomly ordered days: no propofol, target propofol blood concentration 2 μg/ml, and target blood propofol concentration 4 μg/ml. Each day, epidural anesthesia (≈T11 level) was induced, using 2% 2-chloroprocaine (one volunteer received bupivacaine). Thermal manipulations were confined to the legs, and we attempted to maintain upper-body (sensate) skin temperature constant. Propofol was infused by a computer-controlled infusion pump. Volunteers were heated until sweating was observed, then cooled until fingertip vasoconstriction was observed. The sweating threshold was defined as the tympanic membrane temperature triggering sustained evaporative heat loss >40 $g \cdot m^{-2} \cdot h^{-1}$. Similarly, the vasoconstriction threshold was defined as the tympanic membrane temperature triggering a sustained reduction in fingertip blood flow to <0.25 ml/min. Central venous blood was assayed for propofol blood concentration.**

Results: **Increasing propofol concentration produced a linear decrease the vasoconstriction threshold (slope = $-0.53 \pm 0.34°C \cdot \mu g^{-1} \cdot ml^{-1}$; $R^2 = 0.98 \pm 0.04$ [mean ± SD]), but had little effect on the sweating threshold. The interthreshold range was 0.51 ± 0.46°C during epidural anesthesia alone, and increased significantly, by $0.49 \pm 0.31°C \cdot \mu g^{-1} \cdot ml^{-1}$ during propofol administration.**

Conclusions: **Like volatile anesthetics, propofol reduces the vasoconstriction threshold and increases the interthreshold range. However, propofol differs in leaving the sweating threshold unchanged. (Key words: Anesthetics, intravenous: propofol. Anesthesia: epidural. Temperature, regulation: sweating; threshold; vasoconstriction. Thermoregulation.)**

MILD intraoperative hypothermia is common and is associated with increased postoperative morbidity, including myocardial ischemia[1] and reduced resistance to surgical wound infections.[2] Volatile anesthetics contribute to intraoperative hypothermia largely by impairing central thermoregulation.[3] Once triggered, however, thermoregulatory vasoconstriction minimizes further core hypothermia.[4] Typical surgical doses of halothane,[5] enflurane,[6] and isoflurane[7] decrease the vasoconstriction threshold (the core temperature triggering vasoconstriction) by 2–4°C and increase the sweating threshold (the core temperature triggering sweating) by ≈1°C.[8,9] The interthreshold range (core temperatures *not* triggering autonomic thermoregulatory responses) therefore is increased by ≈4°C.

The effects of intravenous anesthetics on thermoregulatory responses in humans are less well known. Barbiturates, taken in overdose, result in abnormal temperature control,[10] and fentanyl with nitrous oxide[11] reduces the vasoconstriction threshold. Hynson *et al.*[12] demonstrated substantial impairment of thermoregulatory vasoconstriction during propofol–nitrous oxide

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Received from the Thermoregulation Research Laboratory, University of California, San Francisco, and the Department of Anaesthesia, Royal Melbourne Hospital, Parkville, Australia. Accepted for publication April 4, 1994. Supported by the Joseph Drown Foundation and by National Institutes of Health grants GM 39723 and GM 49670.

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anesthesia; some volunteers demonstrated no thermoregulatory compensation to core temperatures as low as 33°C. However, several limitations to this study inspired us to reevaluate the thermoregulatory effects of propofol.

First, nitrous oxide has substantial effects on thermoregulatory thresholds itself.[13–15] Second, the core temperature triggering sweating was not measured, and therefore the interthreshold range could not be determined. Third, most volunteers were given a single dose of propofol, so that a dose–response relation was not be established. Finally, and most importantly, core hypothermia was induced by cooling sensate skin.

Skin temperature is an important thermoregulatory afferent signal, reportedly contributing ≈5–20% to overall thermal input.[16–18] Protocols using sensate skin warming and cooling will underestimate the degree to which thermoregulation is impaired by a particular treatment. That is, warming sensate skin will reduce the sweating threshold and cooling sensate skin will increase the vasoconstriction threshold. It is therefore best to keep sensate skin temperature constant when evaluating drug effects on thermoregulation.

The cold intravenous fluid model we developed previously,[19] is not suitable for intravenous agents, because attendant changes in intravascular volume may alter drug distribution. Similarly, a protocol developed by Mekjavic *et al.* cannot be used with anesthetics, because it requires vigorous exercise by subjects immersed in water.[20] We therefore developed a new model in which afferent thermal input from the legs is blocked by epidural anesthesia, and thermal manipulations are restricted to insensate lower-body skin. Using this model, we tested the hypothesis that propofol increases the interthreshold range by raising the sweating threshold and decreasing the vasoconstriction threshold.

Materials and Methods

With approval from the Committee on Human Research at the University of California, San Francisco, we studied six healthy male volunteers. None was obese, was taking medication, or undertook regular strenuous exercise. The volunteers' height was 182 ± 4 cm (mean ± SD), total body mass 80 ± 6 kg, and age 31 ± 6 yr. The lean body mass was 63 ± 4 kg as determined from height (centimeters) and total body mass (kilograms) using the formula[21]: lean body mass = (1.10 × total body mass) − 128 × (total body mass/height)^2.

Volunteers were studied on 3 randomly ordered days within 1 week: control (no propofol), a target propofol blood concentration of 2 μg/ml, and a target propofol blood concentration of 4 μg/ml. On each day, we induced core hyperthermia sufficient to evoke sweating, and subsequently core hypothermia sufficient to evoke peripheral vasoconstriction. Cooling was started at the same time each day, to account for circadian variations.

Protocol

The volunteers fasted for 8 h before arriving at the laboratory; during studies, they were minimally clothed and rested supine on a standard operating room table.

An L2–L3 epidural catheter and a right internal jugular central venous catheter were inserted using standard techniques. An antecubital vein in the nondominant arm was cannulated for fluid and drug administration. Routine anesthetic variables, including blood pressure, heart rate and oxygen saturation were recorded continuously using automatic record-keeping software (IdaCare, Premier Anesthesia Systems, Atlanta, GA).

Ambient temperature was maintained at 23.0 ± 0.4°C. We attempted to maintain upper-body (sensate) skin temperature at 35.5–36.0°C using a Bair Hugger forced-air warmer (Model 300 cover, Model 200 heater, Augustine Medical, Eden Prairie, MN). The torso and upper limbs were wrapped in plastic to prevent evaporative heat loss.

Induction of epidural anesthesia was preceded by 1 h of cutaneous warming to prevent redistribution hypothermia,[22] and we infused 15 ml/kg lactated Ringer's solution. Epidural anesthesia then was induced in 5 volunteers using 2% 2-chloroprocaine (Chloroprocaine HCl, USP, Abbott Laboratories, North Chicago, IL). A test dose of 3 ml with epinephrine 1:100,000 was followed by slow administration of 20 ml without epinephrine to produce a dermatomal level of sensory blockade near T11. Subsequently, the sensory level was maintained with an infusion of 2% 2-chloroprocaine, ≈20 ml · h^{-1}. One volunteer received 15 ml 0.5% bupivacaine followed by two boluses of 5 ml because he had experienced back pain after a previous chloroprocaine anesthetic. When a ≈T11 block did not result, additional anesthetic was given or the catheter replaced, and the study continued after successful epidural blockade was established.

Propofol was infused using a pump (Ohmeda 9000, Ohmeda, Steeton, England) controlled by a computer programmed to target propofol blood concentrations

of 2 and 4 μg/ml. The pharmacokinetic data were derived from a previous study of propofol pharmacokinetics during hypothermia.[23] Combined data for hypothermic and normothermic volunteers were used to program the pump. Airway support was applied as appropriate to the degree of sedation. Oxygen (4 l · min^{-1} *via* nasal cannulae) was administered as necessary to maintain the hemoglobin oxygen saturation > 95%.

Fifteen minutes after the infusion started, the insensate legs were wrapped in plastic and warmed with a circulating-water mattress (Blanketrol II, Maxi-Therm mattress, Cincinnati Sub-Zero, Cincinnati, OH) set to 42°C and a Bair Hugger warmer set to "high" (≈42°C). Lower-limb warming continued until volunteers had sweated for 20 min. Core hypothermia then was induced by decreasing the temperature of the water mattress under the legs to 10°C; also, the legs were exposed to fan-driven air and sprayed with water to produce evaporative cooling. The study ended each day when fingertip vasoconstriction was detected.

Measurements

Control values for all study variables were obtained before the hour of prewarming. Epidural sensory block height was estimated using temperature discrimination, before and after anesthesia, as well as at 30-min intervals on the control day. Block level also was evaluated at 30-min intervals during propofol administration when the volunteers were sufficiently alert to cooperate.

Core temperature was measured at the tympanic membrane (Mon-a-Therm, Mallinckrodt Anesthesiology Products, St. Louis, MO). The aural probe was inserted until felt by the volunteer next to the membrane; appropriate placement was confirmed by gently rubbing the wire. The probe then was taped in position and the canal occluded with cotton. Tympanic membrane temperatures correlate well with distal esophageal temperatures during anesthesia.[24] Area-weighted, upper-body skin temperature was computed from measurements at seven sites and lower-body skin temperature was similarly derived from eight sites, as previously described.[9]

Sweating was quantified on the left upper chest, just below the clavicle, using a ventilated capsule.[8] The sweating threshold was defined as the core temperature triggering sustained sweating > 40 g · m^{-2} · h^{-1}. Absolute right middle fingertip blood flow was quantified using venous-occlusion volume plethysmography at 5-min intervals.[25] The vasoconstriction threshold was defined as the core temperature producing a sustained decrease in fingertip blood flow to <0.25 ml/min. Great-toe temperatures were monitored to confirm vasodilation in the legs.[7] Temperature data were recorded at 5-min intervals using a previously described data-acquisition system.[26]

Central venous blood was sampled for measurement of propofol blood concentration at 15-min intervals. Three-milliliter samples were stored in heparinized tubes at 4°C for as long as 10 weeks (propofol blood concentrations decrease less than 0.2% per week at 4°C) and subsequently analyzed using a high-pressure liquid chromatography assay, modified from the method of Plummer.[27] This assay is linear to at least 20 μg/ml and has a detection limit of 0.025 μg/ml and a coefficient of variation of 4.1% at 2 μg/ml.

Data Analysis

Ambient temperature, humidity, heating and cooling rates, and mean arterial blood pressure and heart rate on each study day were first averaged for each volunteer; the resulting values were then averaged among volunteers. Results for each study day were compared using repeated-measures analysis of variance and Dunnett's *t* tests. Upper-body skin temperatures and propofol blood concentrations at sweating and vasoconstriction thresholds were similarly averaged, then compared with a paired two-tailed *t* test.

Sweating and vasoconstriction threshold temperatures and propofol concentrations for each volunteer were analyzed using linear regression. The average slopes and correlation coefficients for the six volunteers then were computed. Results are presented as mean ± SD. $P < 0.05$ was considered statistically significant.

Results

Induction and maintenance of propofol anesthesia was smooth in all cases; no adverse effects were noted. Volunteers typically were mildly sedated when the target concentration was 2 μg/ml, and deeply sedated (sometimes requiring airway support) when the target concentration was 4 μg/ml. The epidural-induced dermatomal level for loss of temperature discrimination was T11 ± 1 (range T9–T12), and was similar at sweating and vasoconstriction thresholds. The legs remained vasodilated throughout epidural anesthesia in all volunteers, as evidenced by great-toe skin temperatures exceeding ≈30°C. The volunteer who received bu-

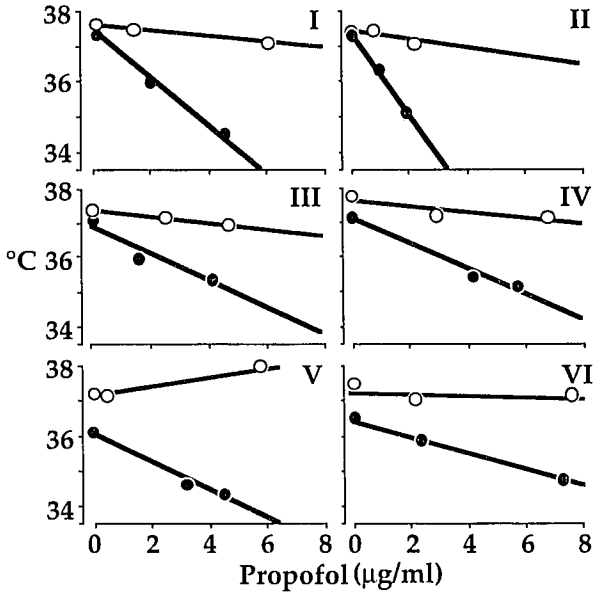

Fig. 1. The effect of increasing propofol blood concentration on the core temperatures triggering sweating (open circles and line) and vasoconstriction (closed circles and line) for the six volunteers. Propofol significantly decreased the vasoconstriction threshold without altering the sweating threshold.

pivacaine (subject 1, fig. 1) had a similar pattern of thermoregulatory impairment to the other volunteers.

Ambient temperature, humidity, mean arterial blood pressure, heart rate, and heating and cooling rates did not differ significantly among the 3 study days. Upper-body skin temperatures were slightly (but significantly) less at the vasoconstriction threshold than the sweating threshold on the 2- and 4-μg/ml days, despite vigorous attempts to maintain the upper-skin temperature at 35.5–36.0°C. However, upper-body skin temperatures were comparable at each threshold on the 3 study days. Propofol blood concentrations were less at the vasoconstriction threshold than at the sweating threshold when the target concentration was 4 μg/ml but were comparable when the target was 2 μg/ml (table 1).

Propofol significantly decreased the core temperature triggering vasoconstriction (slope = −0.53 ± 0.34°C · $\mu g^{-1} \cdot ml^{-1}$; R^2 = 0.98 ± 0.04). In contrast, the sweating threshold did not change significantly with increasing propofol blood concentration (figs. 1 and 2). Whereas the concentration–response relation for both sweating and vasoconstriction was linear in each subject, slopes varied (table 2 and fig. 1). The interthreshold range was 0.5 ± 0.5°C during epidural anesthesia alone, but increased by 0.5 ± 0.3°C · $\mu g^{-1} \cdot ml^{-1}$ during propofol administration.

Discussion

With this study, we introduce a new model for evaluating the thermoregulatory effects of anesthetic drugs. This model takes into account the important contribution of skin temperature to thermoregulatory control, achieving core cooling without altering sensate skin temperature.[20,28] In addition, the vasoconstriction and sweating thresholds at each drug dose are identified in the same subject on the same day.[20,29] The use of linear regression analysis for each response within each subject means drug blood concentrations need not be similar at different thresholds, nor among subjects. This is

Table 1. Study Conditions at Each Propofol Concentration

	Control	2 μg/ml	4 μg/ml
Ambient temp. (°C)	22.7 ± 0.9	22.7 ± 0.6	23.5 ± 0.9
Relative humidity (%)	38 ± 6	34 ± 13	38 ± 5
Mean arterial blood pressure (mmHg)	84 ± 8	75 ± 4	78 ± 7
Heart rate (bpm)	74 ± 11	67 ± 10	67 ± 10
Warning rate (°C/h)	0.6 ± 0.1	0.4 ± 0.1	0.6 ± 0.3
Cooling rate (°C/h)	−1.5 ± 0.4	−1.3 ± 0.4	−0.9 ± 0.3
Upper-body skin temperature at sweating (°C)	36.3 ± 0.2	36.2 ± 0.3	36.2 ± 0.2
Upper-body skin temperature at vasoconstriction (°C)	35.9 ± 0.5	34.9 ± 0.8*	34.9 ± 0.5*
Propofol at sweating threshold (μg/ml)	—	1.7 ± 1.0	5.5 ± 1.9
Propofol at vasoconstriction threshold (μg/ml)	—	2.4 ± 1.2	4.7 ± 1.8†

On the control day, no propofol was given; 2- and 4-μg/ml blood propofol concentrations were targeted on the other two days. BP = blood pressure.

* $P < 0.05$ compared to upper-body skin temperature at sweating threshold.

† $P < 0.01$ compared to propofol concentration at sweating threshold.

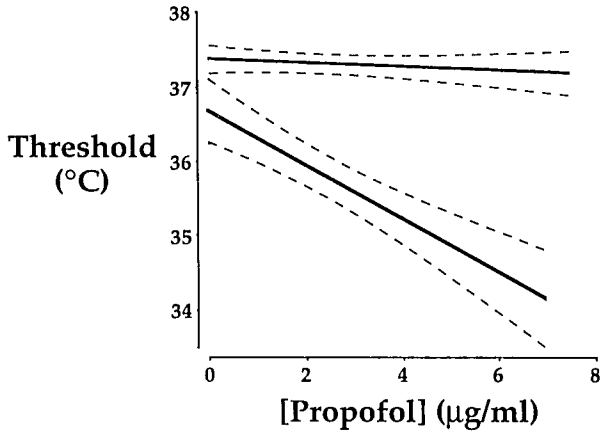

Fig. 2. Propofol produced a linear decrease in the core temperature triggering vasoconstriction (bottom line; dashed lines = 95% confidence limits): regression equation y = −0.365x + 36.69. In contrast, the sweating threshold was not significantly affected (top line; dashed lines = 95% confidence limits): regression equation y = −0.025x + 37.37. Sweating and vasoconstriction thresholds were established in each subject on the same day. Epidural anesthesia provided insensate skin for heating and cooling. Upper-body skin temperature was kept nearly constant throughout.

a critical aspect of the design because it generally is difficult to predict the pharmacokinetic consequences of core temperature perturbations. Furthermore, pharmacokinetic population variability does not introduce variability into the individual calculations of thermoregulatory dose-dependence.

This model has important advantages over our previous model, in which skin temperature is held constant while core temperature is reduced by central venous administration of cold intravenous fluid.[19] Alterations in intravenous anesthetic pharmacokinetics by changes in vascular volume are avoided, making it easier to maintain nearly constant blood concentrations and facilitating interpretation of assay results.

Similarly, the current model has advantages over the method of Mekjavic *et al.*[20] In that protocol, volunteers are immersed in 28°C water to maintain skin temperature constant, exercise vigorously to increase core temperature and subsequently cool passively. This model is obviously unsuitable for evaluating general and regional anesthetics, and the physically unfit or disabled.

The major disadvantage of our model is the requirement for epidural anesthesia, which adds both technical complexity and risk to the study. Furthermore, regional anesthesia complicates assessment of the thermoregulatory effects of the test drug, as regional anesthesia itself has thermoregulatory effects.[30] Complete sensory epidural blockade is crucial to the success of the model, as leg temperature perception may reduce the interthreshold range.[20,28] Some variation in sensory block intensity may account for the small variation in interthreshold ranges on the control day, despite obliteration of consciously perceived leg temperature in all volunteers, and additionally may be a source of variability among volunteers during propofol administration.

Blockade of sympathetic fibers to the legs also is important, as leg vasoconstriction prevents further core cooling,[4] making the study difficult or impossible to complete. Complete sensory blockade, even to T1, does not guarantee complete blockade of preganglionic sympathetic fibers during epidural anesthesia.[31,32] In addition, the level of sympathetic blockade is not necessarily the same as that of sensory blockade.[31,32] Variable relay of preganglionic fibers in the sympathetic chain, and mixing of fibers from diverse sources in perivascular nervous plexuses may account for these phenomena.[33] Fortunately, we were able to keep the legs vasodilated throughout this study, as evidenced by great-toe skin temperatures exceeding 30°C despite substantial leg cooling.[7]

Inclusion of epidural anesthesia in this model also complicates assessment of the thermoregulatory effects of propofol. We confirm previous reports that regional anesthesia alone has significant effects on central thermoregulation,[30] increasing the interthreshold range from normal values near 0.2°C[19] to ≈0.6–0.9°C[30] Our results, therefore, are not applicable to propofol given alone. However, because the epidural block level was similar in each subject on each day, differences among days do result from propofol administration. Thus, the reported slopes of the threshold regressions (dose-dependent thermoregulatory inhibition) likely would be similar without epidural blockade.

Propofol significantly increased the interthreshold range, and did so by linearly decreasing the vasoconstriction threshold. This result confirms and extends the results of Hynson *et al.* for propofol–nitrous oxide. In contrast, the sweating threshold was not significantly altered. This pattern differs distinctly from that produced by volatile anesthetics, which both decrease the vasoconstriction threshold,[7,6] and increase the sweating threshold.[8,9] Thus, for the first time, we have demonstrated a departure from the general paradigm proposed for the thermoregulatory effects of general anesthetics.[34] Confirmation of this

Table 2. Thermoregulatory Thresholds during Propofol Administration

	Sweating		Vasoconstriction	
Volunteer	Slope ($°C \cdot \mu g^{-1} \cdot ml^{-1}$)	r^2	Slope ($°C \cdot \mu g^{-1} \cdot ml^{-1}$)	r^2
1	−0.08	0.98	−0.67	0.99
2	−0.12	0.56	−1.15	1.00
3	−0.09	1.00	−0.38	0.90
4	−0.08	0.76	−0.36	0.98
5	0.14	0.99	−0.40	0.98
6	−0.02	0.14	−0.23	1.00
Mean ± SD	−0.04 ± 0.09	0.74 ± 0.34	−0.53 ± 0.34	0.98 ± 0.04

Propofol significantly decreased the threshold for vasoconstriction but did not alter the sweating threshold.

apparent difference awaits assessment of volatile anesthetics using the same protocol. Although the molecular mechanisms by which anesthetics impair thermoregulation remain unknown, these data suggest that the specific thermoregulatory actions of propofol and the volatile anesthetics differ.

A 4-μg/ml concentration of propofol in blood is 50% of the blood concentration required to prevent movement after surgical incision in 50% of subjects[35] and decreases the vasoconstriction threshold to ≈35°C. Similarly, contrast, 0.5 MAC of isoflurane reduces the vasoconstriction threshold to ≈35°C.[7] Comparisons are complicated, however, because in the isoflurane study,[7] cold intravenous fluid was administered, sentient skin was cooled, vasoconstriction was defined differently, and epidural anesthesia was not used. Nevertheless, our data suggest that propofol and isoflurane comparably reduce the threshold for vasoconstriction.

In contrast, the volatile anesthetics appear to increase the sweating threshold more than does propofol.[8,9] The concentration of isoflurane expected to decrease the vasoconstriction threshold to ≈35°C (0.65%) would increase the sweating threshold to ≈37.5°C.[7,8] Instead, propofol had essentially no effect on the sweating threshold. Once triggered, sweating is remarkably effective at preventing further increases in core temperature.[36] Propofol would thus be a poor choice for sedation or anesthesia when deliberate hyperthermia is planned.

There are several limitations to this study. First, upper-body (sensate) skin temperature proved difficult to maintain during the core hypothermia that was required to trigger vasoconstriction during propofol administration. Despite use of two forced-air warmers and insulating covers, upper-body skin temperature was ≈1.3°C greater during sweating than at the vasoconstriction threshold. However, it is unlikely that this small difference affected our results, especially as the difference was similar on each study day. In previous studies, mean (sensate) skin temperature varied by as much as 10°C at the sweating and vasoconstriction thresholds.[6,9]

Second, the time from sweating to vasoconstriction increased with increasing propofol blood concentration. Because of circadian variation,[37] measured reduction in the vasoconstriction threshold would have been greater had it been evaluated as early in the day as sweating. Third, arterial carbon dioxide concentration was not controlled and likely was somewhat greater during propofol administration than on the control day. However, effects of carbon dioxide on thermoregulation in humans remains controversial. Studies on shivering report no effect (4% carbon dioxide),[38] enhancement (3% carbon dioxide),[39] and inhibition (4.5–6% carbon dioxide).[40] As ventilation was adequate clinically, and as changes associated with hypercarbia, and with circadian rhythms, are small compared with those induced by high-dose propofol,[12] our results probably were not substantially affected by these intrinsic limitations in our model.

Last, our choice of central venous blood sampling may have resulted in falsely increased propofol blood concentrations. However, the 3-day study design precludes the use of arterial sampling, and peripheral venous sampling becomes difficult as subjects vasoconstrict. We believe that positioning of the catheter tip in the distal superior vena cava allowed for adequate mixing.

In conclusion, we present a new model for evaluating thermoregulatory effects of anesthetic drugs. Like volatile anesthetics, propofol reduced the vasoconstriction threshold and increased the interthreshold range. In

contrast to volatile anesthetics, however, propofol did not alter the sweating threshold.

The authors thank Kristen Walter, B.A., and Benjamin Merrifield, B.S., for technical assistance. They thank Ohmeda for loaning a Modulus CD integrated anesthesia machine and infusion pump, Mallinckrodt Anesthesiology Products for donating thermocouples, Hermes Systems for loaning an Idacare automatic record-keeping system, Cincinnati Sub-Zero for loaning a circulating-water mattress, and Augustine Medical for providing the Bair Hugger forced-air warmers and covers.

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