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Non-thermoregulatory Shivering in Patients Recovering from Isoflurane or Desflurane Anesthesia

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Background: **Although cold-induced shivering is an obvious source of postanesthetic tremor, other causes may contribute. Consistent with this theory, the authors had previously identified an abnormal clonic component of postoperative shivering and proposed that it might be nonthermoregulatory. A subsequent study, however, failed to identify spontaneous muscular activity in normothermic volunteers. These data suggested that the initial theory was erroneous or that a yet-to-be identified factor associated with surgery might facilitate shivering in patients after operation. Therefore, the authors tested the hypothesis that some postoperative tremor is nonthermoregulatory.**

Methods: **One hundred twenty patients undergoing major orthopedic operation were observed. They were grouped randomly to receive maintenance anesthesia with nitrous oxide and isoflurane (0.8 ± 0.4%) or desflurane (3.4 ± 1.1%). Twenty patients in each group were allowed to become hypothermic, whereas normal body temperatures were maintained in the others (tympanic membrane temperature exceeding preinduction values). Arteriovenous shunt vasoconstriction was evaluated using forearm-minus-fingertip skin-temperature gradients; gradients less than 0°C identified vasodilation. Postanesthetic shivering was graded by a blinded investigator. Tremor in patients who were normothermic and vasodilated was considered nonthermoregulatory.**

Results: **Thermoregulatory responses were similar after isoflurane or desflurane anesthesia. Approximately 50% of the unwarmed patients shivered. Shivering was observed in 27% of the patients who were normothermic; 55% of this spontaneous muscular activity occurred in vasodilated patients. Among the normothermic patients, 15% fulfilled the authors' criteria for nonthermoregulatory tremor.**

Conclusions: **The incidence of postoperative shivering is inversely related to core temperature. Therefore, it was not surprising that shivering was most common among the hypothermic patients. The major findings, however, were that shivering remained common even among patients who were kept scrupulously normothermic and that many shivered while they were vasodilated. Thus, postoperative patients differ from nonsurgical volunteers in demonstrating a substantial incidence of nonthermoregulatory tremor. (Key words: Clonus; postanesthesia care; recovery duration; thermoregulation; vasoconstriction; temperature; tremor.)**

BODY temperature normally is maintained within 0.2°C of a centrally determined target temperature by efferent responses such as sweating, vasoconstriction, and shivering.[1] General anesthetics, including isoflurane[2] and desflurane,[3] decrease the vasoconstriction and shivering thresholds (triggering core temperatures) by 2-4°C. As a result, unwarmed surgical patients usually become hypothermic.[4] After operation, core temperatures that are less than cold-response thresholds trigger thermoregulatory vasoconstriction and shivering. Thermoregulatory

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shivering is preceded by arteriovenous shunt vasoconstriction because the threshold for shivering is approximately 1°C less than that for vasoconstriction.[5] Consistent with this theory, hypothermic patients usually are "vasoconstricted" and frequently shiver after operation.[6,7**]

Shivering-like tremor, however, reportedly also occurs in normothermic postanesthetic patients,[8-10] rats,[11] and cats.[12] One potential mechanism is fever,[13,14] a response mediated by endogenous pyrogens[15] *via* incompletely understood mechanisms.[**16,17] Many of these cytokines are released by tissue damage. Therefore, it is likely that fever will develop in some surgical patients in the immediate postoperative period. Fever is characterized by a synchronous increase in thermoregulatory response thresholds (a "setpoint" increase).[13] The clinical result is activation of cold defenses at a normal or elevated core temperature. Nonetheless, fever-induced shivering is preceded by arteriovenous shunt vasoconstriction even during anesthesia.[18]

An alternative explanation for spontaneous muscular activity in normothermic patients after operation is nonthermoregulatory tremor, and many such tremors have been identified.[19,20] Consistent with this possibility, electromyographic analysis indicates that tremor in patients recovering from isoflurane anesthesia contains an abnormal 5–7-Hz "bursting" pattern that is virtually identical to that produced by pathologic clonus.[21] This clonic activity differs markedly from the normal 4- to 8-cycles/min "waxing-and-waning" pattern of normal shivering,[22] and it has since been observed in other circumstances.[23] When our original electromyographic study results were published,[21] it seemed likely that the clonic tremor was nonthermoregulatory. However, subsequently we could not demonstrate shivering in normothermic volunteers, although the abnormal clonic tremor pattern was detected again.[24] These data suggest that our initial theory was erroneous or that special factors related to surgery (such as stress or pain) might contribute to the genesis of postoperative tremor.

Accordingly, we tested the hypothesis that some postoperative tremor is nonthermoregulatory. The incidence of nonthermoregulatory tremor was evaluated in patients administered isoflurane or desflurane who were normothermic. For the purpose of this analysis, we considered tremor nonthermoregulatory when it occurred in patients who were "vasodilated" and normothermic (core temperature equaling or exceeding preoperative values). To determine the total incidence of shivering (thermoregulatory and nonthermoregulatory), we also evaluated the incidence of shivering in hypothermic patients.

Methods

After we obtained the approval of the local review board and written informed consent, we studied 120 patients undergoing major elective orthopedic operation. Patients were excluded when they were younger than 18 yr, when American Society of Anesthesiologists physical status exceeded 2, when vasoconstrictor agents were necessary for operation, or when long-term α2-agonists were being taken.

Protocol

All patients were premedicated with 7.5 mg oral midazolam. A venous catheter was inserted into the forearm, and an infusion of lactated Ringer's solution was started. General anesthesia was induced by intravenous administration of 2 μg/kg fentanyl, 0.2 mg/kg etomidate, and 0.5 mg/kg atracurium. Patients were selected randomly to maintenance anesthesia with isoflurane (0.8 ± 0.4%, n = 61) or desflurane (3.4 ± 1.1%, n = 59) in nitrous oxide. Ventilation was adjusted to an end-tidal carbon dioxide pressure near 35 ± 3 mmHg.

The first 40 patients in each anesthetic group were selected randomly, on a 1:1 basis, to receive intraoperative passive insulation or active cutaneous upper-body heating (Warm Touch; Mallinckrodt Anesthesiology Products, St. Louis, MO). The other 40 patients were selected randomly, on a 1:1 basis, to receive desflurane or isoflurane, but they were warmed uniformly during operation to maintain preoperative core temperatures. To compensate for the normal daily circadian increase in body temperature, patients assigned to be normothermic were warmed to a target core temperature exceeding preoperative temperatures by 0.1°C/h.[25] Active warming started just before anesthesia was induced and was discontinued at the end of operation. Postoperative pain was treated with intravenous boluses of the μ-receptor agonist piritramide.

Measurements

During operation and postanesthetic recovery, we recorded heart rate and systolic, mean, and diastolic arterial blood pressures (Dinamap; Critikon, Tampa, FL).

** Blatteis C, Sehic E: Fever: How may circulating pyrogens signal the brain? News in Physiological Sciences 1997; 12:1–9

Table 1. Morphometric and Demographic Characteristics, Temperatures, Duration of Surgery, and Time to Arousal State 1

	Isoflurane		Desflurane	
	Hypothermic	Normothermic	Hypothermic	Normothermic
Age (yr)	54 ± 16	48 ± 17	54 ± 17	43 ± 19
Gender (male/female)	10/14	11/26	6/12	16/25
Weight (kg)	71 ± 15	74 ± 15	75 ± 13	71 ± 16
Height (cm)	169 ± 8	170 ± 11	167 ± 9	169 ± 10
Preoperative core temperature (°C)	36.9 ± 0.5	36.7 ± 0.5	36.9 ± 0.6	36.5 ± 0.4
Preoperative mean skin temperature (°C)	33.6 ± 0.6	34.0 ± 0.9	33.1 ± 0.6	33.7 ± 0.7
Duration of surgery (min)	165 ± 87	138 ± 88	144 ± 51	145 ± 63
Postoperative core temperature (°C)	35.2 ± 0.6*	36.8 ± 0.5†	35.5 ± 0.5*	36.8 ± 0.6‡
Postoperative mean skin temperature (°C)	32.3 ± 0.5*	34.7 ± 1.0†	32.5 ± 0.8*	34.5 ± 1.1‡
Time to arousal score 1 (min)	35 ± 21	20 ± 10†	16 ± 7†	12 ± 6†,§
Piritramid during the first postanesthetic hour	6.9 ± 8.6	3.8 ± 6.3	6.3 ± 8.6	4.8 ± 5.6

Data are mean ± SD.

* $P < 0.05$ versus preoperative values.

† $P < 0.05$ versus isoflurane/hypothermic.

‡ $P < 0.05$ versus desflurane/hypothermic.

§ $P < 0.05$ versus isoflurane/normothermic.

End-expiratory anesthetic gas concentrations after extubation were measured from a sealed face mask (Capnomac; Datex, Helsinki, Finland). Core temperature was recorded from the tympanic membrane, and mean skin temperatures were calculated from measurements at the chest, arm, thigh, and calf (Mallinckrodt Anesthesiology Products).[26] In a preliminary study (data not shown), we confirmed that forearm-minus-fingertip skin-surface temperature gradients[27] rapidly indicate postoperative vasoconstriction, even in patients who are actively warmed during operation. Thus, we used skin-temperature gradients to evaluate vasoconstriction; gradients less than 0°C indicated vasodilation.

Postanesthetic shivering was graded by an investigator blinded to type of anesthesia, group assignment, and core and skin temperatures using a four-point scale (0 = no shivering; 1 = intermittent, low-intensity shivering; 2 = moderate shivering; 3 = continuous, intense shivering). A three-lead electrocardiographic recording was adjusted so that 1 μV produced a 40-mm trace amplitude to objectively document shivering activity. Similar to previous studies,[28] shivering artifacts on the electrocardiographic recording were scored by a blinded investigator as no artifact; low-intensity shivering; moderate shivering; and continuous, intense shivering. Measurements were recorded during operation at 15-min intervals and subsequently for 1 h after operation in 5-min intervals. Patient arousal state was assessed by patient response to the verbal command "Open your eyes and lift your arms." Absent or incomplete responses were graded as arousal state zero, and prompt and appropriate responses were graded as arousal state one.

Data Analysis

Spontaneous muscular activity in patients who were normothermic (core temperature ≥ preoperative value) and vasodilated was considered nonthermoregulatory. Continuous, normally distributed variables were analyzed using one-way analysis of variance and Scheffé's F test. Changes during time within each group were evaluated using repeated-measures analysis of variance and Scheffé's F test. Differences between the groups were compared with unpaired, two-tailed Student's *t* tests. Descriptive (categoric) variables were analyzed using a chi-squared test. Data are expressed as mean ± SD; $P < 0.05$ was considered significant.

Results

Morphometric characteristics and the duration of operation were similar among the groups. The patients in the isoflurane/hypothermia group took the most time to reach an arousal score of one. In addition, the desflurane/normothermia patients reached an arousal score of one significantly more quickly than those in the isoflurane/normothermia group (table 1).

Hemodynamic responses were similar among the four treatment groups. No differences were found in systolic, mean, or diastolic arterial blood pressures during the observation period. Heart rates were slightly faster dur-

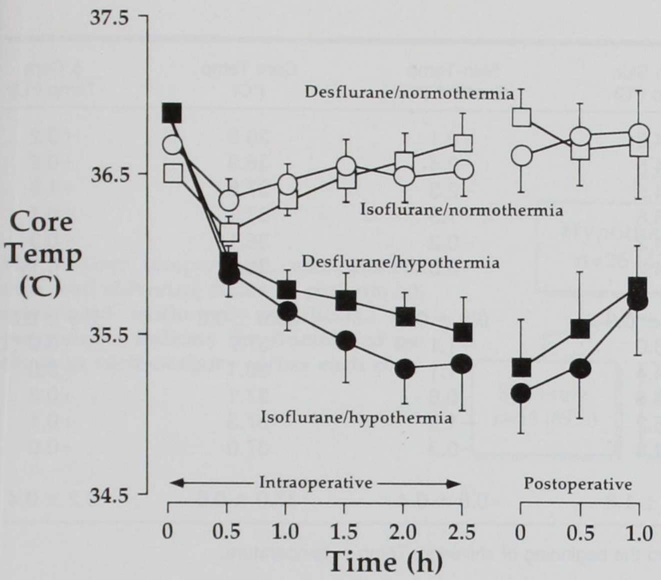

Fig. 1. Tympanic membrane (core) temperatures in patients assigned to receive active warming (n = 80) and passive insulation (n = 40). The passively insulated patients were significantly colder at all times after 30 elapsed min. Postoperative core temperatures in the hypothermic patients increased approximately 0.5°C/h. Data are presented as mean ± SD.

ing normothermic desflurane anesthesia than during normothermic isoflurane anesthesia; however, the differences were not clinically important. For example, the maximum heart rate during desflurane anesthesia was 100 beats/min in normothermic patients and was 103 beats/min in hypothermic patients.

Preinduction tympanic membrane temperatures were comparable in the four groups. According to the protocol, patients assigned to extra warming remained normothermic, whereas those warmed passively became hypothermic. After operation, core temperatures increased approximately 0.5°C/h in the hypothermic patients (fig. 1). Intraoperative and postoperative mean skin-surface temperatures were near normal in the two unwarmed groups and were approximately 2°C higher in the actively warmed patients (fig. 2). The end-expiratory volatile anesthetic concentration at the beginning of postanesthetic shivering was approximately 0.1 minimum alveolar concentration in patients administered each anesthetic (table 2).

During isoflurane anesthesia, 25 of 35 normothermic patients (71%) were vasodilated (skin-temperature gradients < 0°C), and 34% of the normothermic patients remained in dilation after operation. In contrast, 18 of 26 (69%) unwarmed isoflurane patients were vasoconstricted during recovery. During desflurane anesthesia, 37 of 39 normothermic patients (95%) were vasodilated, and 85% of the normothermic patients remained in dilation after operation. In contrast, 18 of 20 (90%) unwarmed patients administered desflurane were vasoconstricted during recovery.

Seventy patients showed neither electrocardiographic nor visual tremor. Forty-nine patients showed both electrocardiographic and visual tremor. Only one patient showed visual tremor without concomitant electrocardiographic tremor, and none had electrocardiographic tremor without visual tremor. The sensitivity of electrocardiographic detection of tremor was 98%, and the specificity of this technique was 100%.

After isoflurane anesthesia, 18 of 26 unwarmed patients shivered (69%), but only 12 of 35 actively warmed patients (34%) shivered ($P < 0.05$). After desflurane anesthesia, 11 of 20 unwarmed patients shivered (55%), but only 8 of 39 actively warmed patients (21%) did so ($P < 0.05$). The overall shivering incidence was similar with isoflurane and desflurane anesthesia.

Among the 37 isoflurane-anesthetized patients assigned to receive active warming, 35 had immediate postoperative temperatures that exceeded preinduction values. Among these normothermic patients, 12 patients shivered and 5 were vasodilated and shivered. Thus, shivering (nonthermoregulatory) was observed in 5 of 12 normothermic and vasodilated patients; this repre-

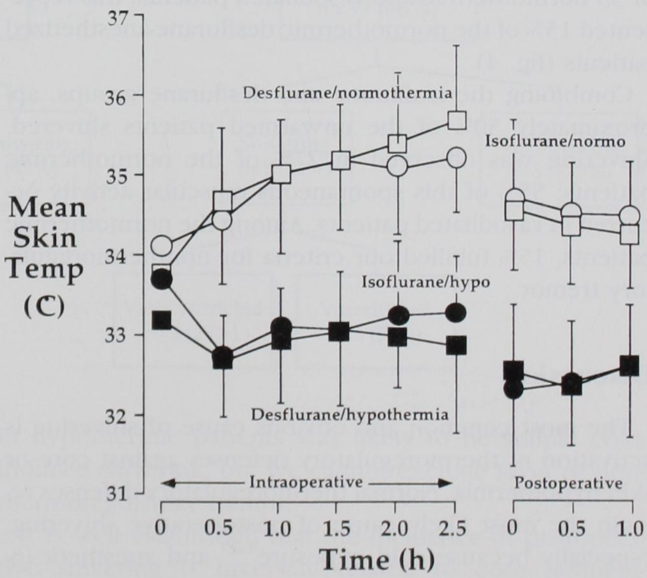

Fig. 2. Mean skin temperatures in patients assigned to receive active warming (n = 80) and passive insulation (n = 40). The passively insulated patients were significantly colder at all times after 15 elapsed min. Data are presented as mean ± SD.

Table 2. Postoperative Normothermic, Vasodilated Patients

End-tidal [anesthetic] (MAC)	Elapsed Time (min)	Shivering Grade (I–III)	Mean Skin Temp (°C)	Skin-Temp Gradient (°C)	Core Temp (°C)	Δ Core Temp (°C)
Desflurane 0.05	10	I	34.3	−0.1	36.8	+0.2
Desflurane 0.08	30	I	34.5	−0.4	36.9	+0.2
Desflurane 0.05	25	II	34.5	−2.3	37.6	+1.3
Desflurane 0.02	40	II	33.8	−1.5	37.3	+0.7
Desflurane 0.18	5	II	34.2	−0.2	36.1	+0.3
Desflurane 0.09	10	II	34.0	−0.5	36.5	+0.1
Mean ± SD						
0.07 ± 0.03	20 ± 14	—	34.2 ± 0.3	−0.8 ± 0.9	36.9 ± 0.5	0.5 ± 0.5
Isoflurane 0.13	55	II	33.0	−1.1	37.7	+0.9
Isoflurane 0.17	40	I	34.4	−1.1	36.1	+0.0
Isoflurane 0.20	10	I	36.6	−0.6	37.1	+0.2
Isoflurane 0.04	15	I	35.2	−1.0	37.3	+0.1
Isoflurane 0.10	20	I	34.8	−0.3	37.0	+0.0
Mean ± SD						
0.13 ± 0.06	28 ± 19	—	34.8 ± 1.3	−0.8 ± 0.4	37.0 ± 0.6	0.2 ± 0.4

Δ Core Temp = difference of core temperature before induction of anesthesia and the beginning of shivering; Temp = temperature.
None of the values differed significantly in the desflurane and isoflurane patients.

sented 14% of the normothermic patients who received isoflurane (fig. 3).

Among the 41 patients who received desflurane and who were assigned to active warming, 39 had immediate postoperative temperatures that exceeded preinduction values. Among these normothermic patients, 12 patients shivered and 6 were vasodilated and shivered. Therefore, shivering (nonthermoregulatory) was observed in 6 of 33 normothermic and vasodilated patients; this represented 15% of the normothermic desflurane-anesthetized patients (fig. 4).

Combining the isoflurane and desflurane groups, approximately 50% of the unwarmed patients shivered. Shivering was observed in 27% of the normothermic patients; 55% of this spontaneous muscular activity occurred in vasodilated patients. Among the normothermic patients, 15% fulfilled our criteria for nonthermoregulatory tremor.

Discussion

The most common and obvious cause of shivering is activation of thermoregulatory defenses against core or skin hypothermia. Normal thermoregulatory defenses remain the most likely cause of postoperative shivering, especially because cold exposure[4,29] and anesthetic-induced thermoregulatory impairment[2,3] make many patients hypothermic. Nonetheless, there is a fairly strong clinical consensus that perioperative shivering occurs in at least some normothermic patients.[8–11] Perhaps as a consequence, postanesthetic shivering has been attributed to many nonthermoregulatory causes, including decreased sympathetic nervous system activity,[30] pain,[31] administration of anesthetic drugs,[32] loss of descending control,[20] adrenal suppression,[33] respiratory alkalosis,†† and release of endogenous pyrogens.[34]

Several studies confirm normothermic shivering,[8–11] whereas others do not.[4,35] The clinical studies, however, uniformly failed to record preoperative temperature and to strictly define *normothermia* as a valid core temperature equaling or exceeding individual initial values. (Using a general definition of normothermia, such as 36°C, is insufficient because body temperature always exceeds this value—and exceeds it by nearly 1.5°C in the mid afternoon, when many operations are concluded.[25]) Furthermore, none of these studies simultaneously evaluated thermoregulatory vasoconstriction, which is the key factor in distinguishing cold-induced shivering from shivering associated with fever or nonthermoregulatory causes.

Critical aspects of our protocol included a strict definition of normothermia and concurrent evaluation of vasomotor status. These measurements allowed us to identify nonthermoregulatory tremor because the shivering threshold (triggering core temperature) is at least

†† Flacke JW, Flacke WE: Inadvertent hypothermia: Frequent, insidious, and often serious. Seminars in Anesthesia 1983; 2:183–96

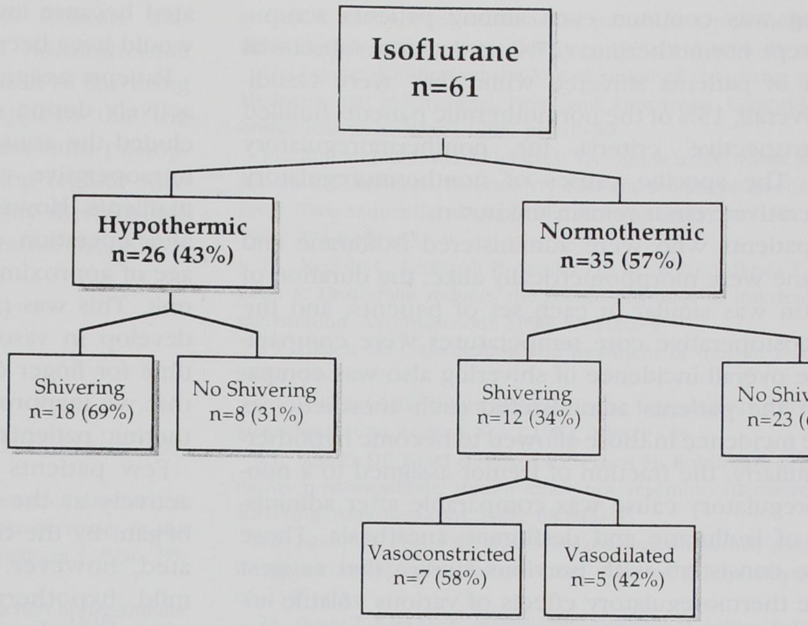

Fig. 3. Core temperature, vasoconstriction, and shivering status in patients administered isoflurane anesthesia. The percentages indicate the fraction of patients in each category across each row.

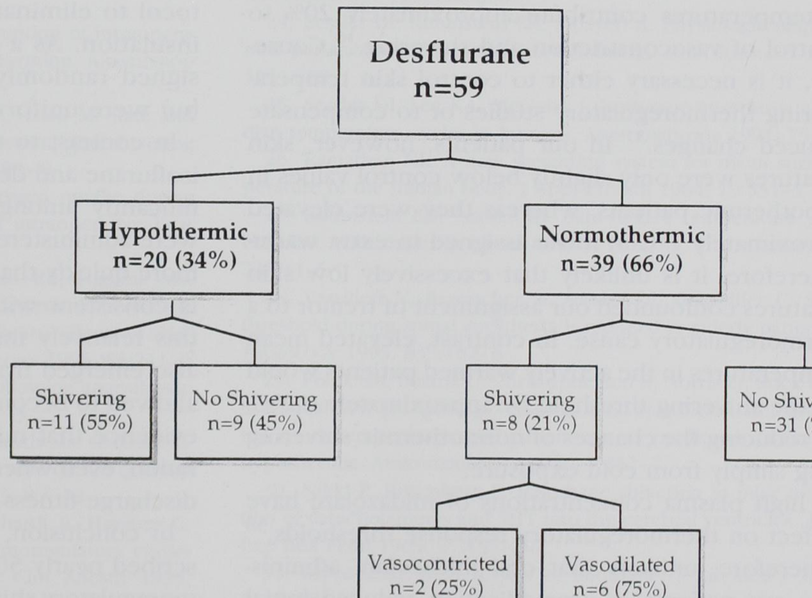

Fig. 4. Core temperature, vasoconstriction, and shivering status in patients administered desflurane anesthesia. The percentages indicate the fraction of patients in each category across each row.

1°C below normal body temperature, and vasoconstriction always precedes normal shivering.[5] In contrast, we cannot assign specific causes to the other response patterns. For example, shivering in normothermic, vasoconstricted patients might result from a febrile elevation of the setpoint but could just as well have been nonthermoregulatory tremor combined with stress-induced vasoconstriction. Similarly, spontaneous muscular activity in hypothermic patients was likely to be simple cold-induced shivering, but we cannot exclude fever or nonthermoregulatory tremor.

It is well established that the incidence of postoperative shivering is inversely related to core temperature.[7,32,35] Therefore, it was hardly surprising that shivering was most common among the hypothermic patients (≈50%). Our major finding, however, was that shivering was common even among patients scrupulously kept normothermic (27%) and that a substantial fraction of patients shivered while they were vasodilated. Overall, 15% of the normothermic patients fulfilled the prospective criteria for nonthermoregulatory tremor. The specific causes of nonthermoregulatory postoperative tremor remain unknown.

The patients who were administered isoflurane and desflurane were morphometrically alike, the duration of operation was similar in each set of patients, and the initial postoperative core temperatures were comparable. The overall incidence of shivering also was comparable in the patients administered each anesthetic, as was the incidence in those allowed to become hypothermic. Similarly, the fraction of tremor assigned to a nonthermoregulatory cause was comparable after administration of isoflurane and desflurane anesthesia. These data are consistent with previous studies that suggest that the thermoregulatory effects of various volatile anesthetics are more notable for the similarities than for the differences.[2,3]

Skin temperatures contribute approximately 20% to the control of vasoconstriction and shivering.[36] Consequently, it is necessary either to control skin temperature during thermoregulatory studies or to compensate for induced changes.[37] In our patients, however, skin temperatures were only slightly below control values in the hypothermic patients, whereas they were elevated by approximately 1°C in those assigned to extra warming. Therefore, it is unlikely that excessively low skin temperatures confounded our assignment of tremor to a nonthermoregulatory cause. In contrast, elevated mean skin temperatures in the actively warmed patients would reduce the shivering threshold by approximately 0.2°C, further reducing the chances of normothermic shivering resulting simply from cold exposure.

Even high plasma concentrations of midazolam have little effect on thermoregulatory response thresholds.[38] It is, therefore, unlikely that oral midazolam administered to our patients as premedication reduced initial core temperatures by any significant amount.[39] Initial core temperatures near 36.8°C are consistent with this theory because the values were similar to those observed in unpremedicated volunteers[5,36] and patients.[40] Electromyographic tremor analysis probably would have helped to characterize nonthermoregulatory tremor. Similarly, measurements of autonomic nervous system activation, pain, and circulating concentrations of endogenous pyrogens might have helped to identify specific causes of this tremor. However, none of these factors was evaluated because including them in this exploratory study would have been difficult.

Patients assigned to be normothermic were warmed actively during operation. In most cases, warming included the arms, which would invalidate evaluation of intraoperative vasoconstriction with skin-temperature gradients. However, none of the patients was warmed after operation, and tremor first appeared after an average of approximately 25 min in the postanesthesia care unit. This was plenty of time for positive gradients to develop in vasoconstricted patients because the half-time for finger cooling is only 6.6 min.[27] It is unlikely that we inappropriately ascribed tremor in the normothermic patients to a nonthermoregulatory cause.

Few patients undergoing operation were warmed actively at the Eppendorf Hospital when this study began. By the time the initial 80 patients were evaluated, however, the evidence had accumulated that mild hypothermia adversely affected patient outcome.[40,41] Furthermore, maintaining normothermia had become routine. Therefore, we modified the protocol to eliminate randomized assignment to passive insulation. As a result, the final 40 patients were assigned randomly to receive isoflurane or desflurane but were uniformly warmed.

In contrast to the similar thermoregulatory effects of isoflurane and desflurane, emergence times differed significantly among the treatment groups. Patients who were administered desflurane reached arousal state one more quickly than those administered isoflurane, which is consistent with the rapid pulmonary elimination of this relatively insoluble vapor. Normothermic patients also emerged from anesthesia more quickly than those allowed to become hypothermic. This is consistent with evidence that mild hypothermia prolongs recovery duration, even when core temperature is not a criterion for discharge fitness.[42]

In conclusion, postanesthetic shivering was first described nearly 50 yr ago.[43] Although cold-induced thermoregulatory shivering is an obvious cause, the phenomenon also has been attributed to many other causes, although none has been documented adequately. In 1988, we identified an abnormal clonic tremor pattern in postoperative patients and proposed that at least one tremor component might be nonthermoregulatory.[21] A subsequent study, however, failed to identify any shivering-like activity in normothermic volunteers.[24] These more recent data suggest that our initial theory was erroneous, or that special factors related to surgery (such as stress or pain) might contribute to the genesis of postoperative tremor. Our current data indicate that postoperative shivering is common in normothermic patients; furthermore, a substantial fraction of shivering is nonthermoregulatory. Therefore, it appears that the distinction between nonsurgical volunteers and postoperative patients is critical in the following regard: shivering-like tremor in volunteers is uniformly thermoregulatory, whereas considerable postoperative tremor is not. Le plus ça change . . . .

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