

Appropriate thermal manipulations eliminate tremors in rats recovering from halothane anesthesia

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Grahn, D. A., M. C. Heller, J. E. Larkin, and H. C. Heller. Appropriate thermal manipulations eliminate tremors in rats recovering from halothane anesthesia. *J. Appl. Physiol.* 81(6): 2547–2554, 1996.—Tremors are common in mammals emerging from anesthesia. To determine whether appropriate thermal manipulations immediately before emergence from anesthesia are sufficient to eliminate these tremors, electroencephalographic (EEG) and electromyographic (EMG) activities, hypothalamic temperature (T_{hy}), and O_2 consumption were monitored in 12 rats recovering from halothane anesthesia under three thermal regimes. EEG and EMG activities were recorded throughout anesthesia and served as feedback signals for controlling anesthetic depth. During anesthesia, T_{hy} was either 1) allowed to fall to 32–34°C, 2) maintained at 37–39°C, or 3) allowed to fall to 32–34°C and then raised to 37–39°C. When hypothermic emergence from anesthesia, all of the animals exhibited postanesthetic tremors that persisted until T_{hy} values returned to normothermia. None of the animals expressed postanesthetic tremors when normothermic on emergence from anesthesia. In addition, the time between emergence from anesthesia (as determined by EEG/EMG parameters) and the initiation of coordinated motor activities was significantly decreased in the normothermic animals.

thermoregulation; anesthetic effect; electroencephalographic activity; electromyographic activity; recovery time

THE MAMMALIAN THERMOREGULATORY SYSTEM maintains an organism's thermal core¹ within normothermy² (14). Temperatures of peripheral tissues (including the skin) are more thermally labile and can vary according to the ambient temperature and the thermal demands of the body core. Vasomotor tone, the primary mechanism for defending core temperature against both metabolic and environmental thermal challenges, controls the heat flux between the body core and peripheral tissues (and thus the environment): vasoconstriction decreases heat transfer between the body core and periphery, whereas vasodilation increases heat transfer. When vasomotor responses are not sufficient to maintain the desired core temperatures, thermogenic or thermolytic mechanisms are activated. Anesthesia dramatically suppresses thermoregulatory function: thermogenic, thermolytic, and vasomotor responses to external thermal challenges are impaired (7, 22, 25). When anesthesia is induced, motor tone and metabolic rate decrease, and

¹ The inner tissues of the body having temperatures that are not changed in their relationship to each other by circulatory adjustments and changes in heat dissipation to the environment that affect the thermal shell of the body (15).

² The condition in which the core temperature of a temperature regulator is within the range associated with the normal resting condition of the species in a thermoneutral environment (15).

peripheral vasodilation occurs. During maintenance of anesthesia, there is a dose-dependent depression in the core temperature threshold for peripheral vasoconstriction (27). Thus core temperature becomes vulnerable to ambient temperature influences during anesthesia.

Conversely, body temperature affects the potency of volatile anesthesia. The concentration of an anesthetic agent necessary to render an individual insensible to noxious stimuli is directly correlated with core temperature: as core temperature decreases, less anesthesia is needed to maintain a constant anesthetic effect (7, 21, 29). A standard for comparing the potency of various volatile anesthetics is the minimum alveolar concentration (MAC; volume percent at 1 atmosphere) necessary to prevent gross muscular movement in response to a painful stimulus in 50% of the subject population (8). MAC values are useful for intra- and interspecies comparisons of the potencies of different volatile anesthetics and provide guidelines for clinically useful anesthetic dosage ranges. However, within the clinically relevant dose ranges, there can be considerable variability in the effect of a given concentration of anesthesia among different individuals (6, 28). Therefore, to maintain a constant anesthetic effect in an individual while manipulating core temperature (and thus, anesthetic potency), it was desirable to utilize a rapid-response feedback signal to assess anesthetic effect and enable appropriate adjustments in anesthetic concentration as core temperature changed. Electroencephalogram (EEG) and electromyogram (EMG) activities provided such a feedback signal. In general, EEG patterns are affected by volatile anesthetics in a dose-dependent manner: an increase in depth of anesthesia produces a slowing and an increase in voltage, with periods of electrical silence appearing at deeper anesthetic levels (11). Muscle relaxation (decreased EMG tone) also increases with increasing volatile anesthetic dose (5). Appropriate manipulations of the concentration of administered anesthetic in response to changes in the EEG and EMG patterns allowed for precise control of the anesthetic effect in individual subjects under varying thermal conditions.

Because most anesthetic procedures are conducted in environments comfortable for clothed humans, decreases in core temperatures are commonly associated with extended anesthesia. Hypothermia³ has both long- and short-term adverse effects on individuals recovering from surgical interventions. Long-term effects of perioperative hypothermia include increased incidence of wound infection, delayed wound healing (i.e., time to

³ The condition when core temperature is below the set range specified for the normal active state of the species (15).

suture removal), and retarded recovery of function (i.e., duration of hospitalization in humans) (18). An obvious short-term effect of perioperative hypothermia is postanesthetic tremors, characterized by spontaneous increases in both clonic and tonic EMG activity and elevated metabolic rate (3, 10, 23). Risks associated with these tremors include increased demands on the cardiovascular system (increased O_2 consumption and vascular resistance), hypoxemia, wound dehiscence, dental damage, and disruption of delicate surgical repairs (2, 16–18, 22). Even mild hypothermia that does not induce tremors can induce peripheral vasoconstriction, which may adversely affect recovery from surgery (18).

Whether the maintenance of normothermy throughout anesthesia is necessary to prevent the detrimental effects of hypothermia is not clear. It has not been determined whether postanesthetic tremors and (presumably) other adverse effects are responses to hypothermia during anesthesia per se or to hypothermia on emergence from anesthesia. While seemingly a trivial distinction, this determination could have a profound effect on how body temperature should be manipulated during prolonged surgical procedures to minimize both the duration and trauma of postsurgical recovery. It may be optimal to allow core temperature to decrease during anesthesia to reduce anesthetic requirements and then rewarm the individuals during emergence from anesthesia to reduce postanesthetic trauma. The hypothesis that core temperature at the time of emergence from anesthesia determines the incidence of postanesthetic tremors was tested by comparing EMG activity and O_2 consumption of rats recovering from halothane anesthesia during which the animals were either rendered hypothermic, maintained normothermic, or rendered hypothermic but rewarmed to normothermy before termination of anesthesia.

METHODS

The experiments were conducted on 12 adult Wistar rats (males, weighing 250–450 g; Simonson Laboratories, Gilroy, CA). The animals were maintained at 22–24°C under a 12:12-h light-dark photoperiod (lights on at 0800) and given ad libitum access to food and water. Each animal was surgically implanted with an EEG/EMG recording array and a reentry tube for thermocouple access to the hypothalamic region. The EEG electrodes were located bilaterally 2 mm off midline and adjacent to bregma and lamda. The EMG electrodes were inserted in the neck muscle. The sealed end of the reentrant tube was stereotaxically placed 10 mm below the top of the skull, 1 mm posterior and 1 mm lateral of bregma. The entire assembly was cast in dental acrylic (for details see Ref. 13). After surgery, the animals were allowed to recover for at least 7 days.

Frontal-occipital EEG, raw EMG, and integrated EMG activities, as well as four temperatures, were monitored throughout the experiment, and O_2 consumption was measured during recovery from anesthesia. The EEG and EMG signals were recorded on polygraph paper (5 mm/s, Grass model 7E polygraph) and, during recovery from anesthesia, the EEG was computer scored in 10-s epochs as either synchronized: high amplitude ($>100 \mu V$), low frequency (1–4 Hz dominated) activity characteristic of slow-wave sleep

(SWS-like) or desynchronized: low amplitude ($<75 \mu V$), high frequency (5–15 Hz dominated), characteristic of waking and rapid-eye-movement sleep (W-like). Copper-constantin thermocouples were used to monitor hypothalamic temperature (T_{hy}) throughout the experiments; skin, rectal, and water blanket temperatures during anesthesia; and ambient temperature postanesthesia. O_2 consumption was determined by measuring changes in O_2 content of a 1 l/min airstream that passed through the chamber in which the animal was housed during recovery. The O_2 content and temperature data were collected at 10-s intervals. Supplemental programs converted changes in O_2 content of the airstream to metabolic rate.

The EMG activity was quantified as the averaged summed voltage/time interval by processing the raw EMG signal through an integrator (Grass model 7P3, 0.5 s time constant). The EMG is a time-variant electrical signal that approximates a complex sine-wave function oscillating around a baseline. The integrated EMG value is the summed absolute area under the curve relative to baseline in a fixed time interval and is proportional to the amount of ongoing bioelectric activity in that time interval: the greater EMG activity, the greater the voltage output of the integrator. The output voltage relative to the input is determined by the gain (voltage amplification) and the time constant (time interval) of the integrator. However, because the waveforms of EMG signals are aperiodic and variable, it is virtually impossible to quantify the integrated EMG in absolute terms. Therefore, the gain and time constant of the integrator were set so that the output ranged between 0 and 5 V and the settings remained constant throughout the experiment. Thus, within an animal, the integrated EMG provided a means for quantifying the relative changes in EMG activity. The integrated EMG signal was sampled at 10-s intervals and stored along with the other data.

On the day of an experiment, the animal was placed in a small acrylic box (15 × 15 × 15 cm) and exposed to a halothane vapor-air mixture (~4% halothane). Immediately after the induction of anesthesia, the animal was removed from the enclosure and subsequently anesthetized through a mask that fit over its snout. The EEG and EMG electrodes were connected to the recording apparatus, and thermocouples were inserted into the reentrant tube to measure T_{hy} and into the rectum (1.5–2.0 cm) for an additional measure of core temperature during anesthesia. During anesthesia, T_{hy} was controlled by manipulating skin temperature. The anesthetized animal was wrapped in a water-perfused blanket; the temperature of the perfusate stream was controlled by adjusting the proportional flow from hot (50°C) and cold (15°C) water baths.

EEG and EMG activities were used as feedback signals for regulating anesthetic depth. Induction of halothane anesthesia was accompanied by a decrease in overall EMG activity and a transformation in the EEG from a W-like high-frequency-low-amplitude pattern into a SWS-like low-frequency-high-amplitude pattern. A light surgical plane of halothane anesthesia (~1 MAC) is characterized by a SWS-like EEG pattern and very low EMG activity. At this anesthetic plane, the application of a noxious stimulus, or a slight decrease in anesthetic concentration, caused an elevation in tonic EMG activity without an accompanying gross motor response and/or a desynchronization of the EEG pattern (to a W-like pattern). As anesthesia deepened, the SWS-like EEG pattern was interrupted by periods of electrical silence (burst suppression). The burst-suppression ratio (the ratio of time the EEG was suppressed vs. the epoch time) was directly correlated with anesthetic concentration: the higher the anesthetic level, the greater the proportion of electrical

silence in the EEG (20). Decreases in core temperature at a fixed anesthetic plane affected the EEG/EMG pattern in a manner similar to increasing the anesthetic dose. At a fixed anesthetic concentration, a SWS-like EEG pattern in a normothermic anesthetized individual will convert into a burst-suppression EEG pattern as core temperature falls, with the burst-suppression ratio increasing as core temperature decreases (19, 13). Thus, to maintain a constant anesthetic effect, it was necessary to decrease the concentration of administered anesthetic as core temperature decreased (Fig. 1). After the initial induction of anesthesia and attachment of the EEG/EMG cables, the anesthetic gas mixture was continuously adjusted to maintain a SWS-like EEG pattern and low EMG activity. If the tonic EMG activity increased (or the EEG desynchronized to a W-like pattern), the halothane-to-air ratio was increased. If the EEG pattern transformed into a burst-suppression pattern, the halothane-to-air ratio was decreased.

A repeated-measures experimental design was used to determine whether core temperature affected the incidence of postanesthetic tremors. On alternate days, eight animals were randomly subjected to 1–1.5 h of halothane anesthesia under three thermal conditions. 1) Hypothermia: the animals were placed on a metal plate at room temperature (22–24°C) for 1 h. 2) Normothermia: the animals were maintained at $T_{hy} = 36\text{--}39^\circ\text{C}$ for 1 h. 3) Rewarmed: the animals were placed on a metal plate (22–24°C) for 1 h and then rewarmed to $T_{hy} = 37\text{--}39^\circ\text{C}$ before termination of the anesthesia (see Fig. 2). In a separate set of experiments, four animals were rendered hypothermic ($T_{hy} = 32\text{--}34^\circ\text{C}$) for 4 h and rewarmed to $T_{hy} = 37\text{--}39^\circ\text{C}$ while under anesthesia. During recovery from anesthesia, the animals were maintained in a small metabolic chamber with a clear acrylic lid at room temperature (22–24°C). The animals were monitored for 1.5–2 h after the termination of anesthesia.

The animals were vulnerable to external thermal influences until they emerged from anesthesia (Fig. 2). If heat was not applied to an anesthetized animal, T_{hy} decreased to 32–33°C within 1 h. When the animals were maintained at normothermy ($36^\circ\text{C} < T_{hy} < 39^\circ\text{C}$) throughout anesthetic exposure or rewarmed before termination of anesthesia, there was an abrupt decrease in T_{hy} after the termination of the anesthesia and return to ambient temperature. This drop in T_{hy} always occurred before emergence from anesthesia as determined by EEG and EMG criteria. Therefore, it was necessary for the animals to be at $38^\circ\text{C} < T_{hy} < 39^\circ\text{C}$ at the termination of the anesthetic administration and removal of the water-perfusion blanket to ensure that they were normothermic on emergence from anesthesia.

Two stages of recovery from anesthesia were judged: emergence from anesthesia and restoration of behavioral activity (behavioral recovery). Emergence from anesthesia was defined as an increase in tonic EMG activity and a change in the EEG from a SWS-like pattern to a W-like pattern. Behaviorally, recovery occurred when the animal rose from a prone position and initiated coordinated movements. The time intervals from termination of anesthesia to emergence and behavioral recovery were measured in all animals. Time and T_{hy} data were subjected to a repeated-measures analysis of variance, and the Scheffé's method was employed for testing differences between pairs of means.

After termination of anesthesia, 1-min averages of integrated EMG, T_{hy} , and O_2 consumption were calculated for each animal. The recording sessions after termination of anesthesia were subdivided into three periods. 1) Emergence: termination of anesthesia to EEG/EMG-defined emergence from anesthesia; 2) recovery: EEG/EMG-defined emergence

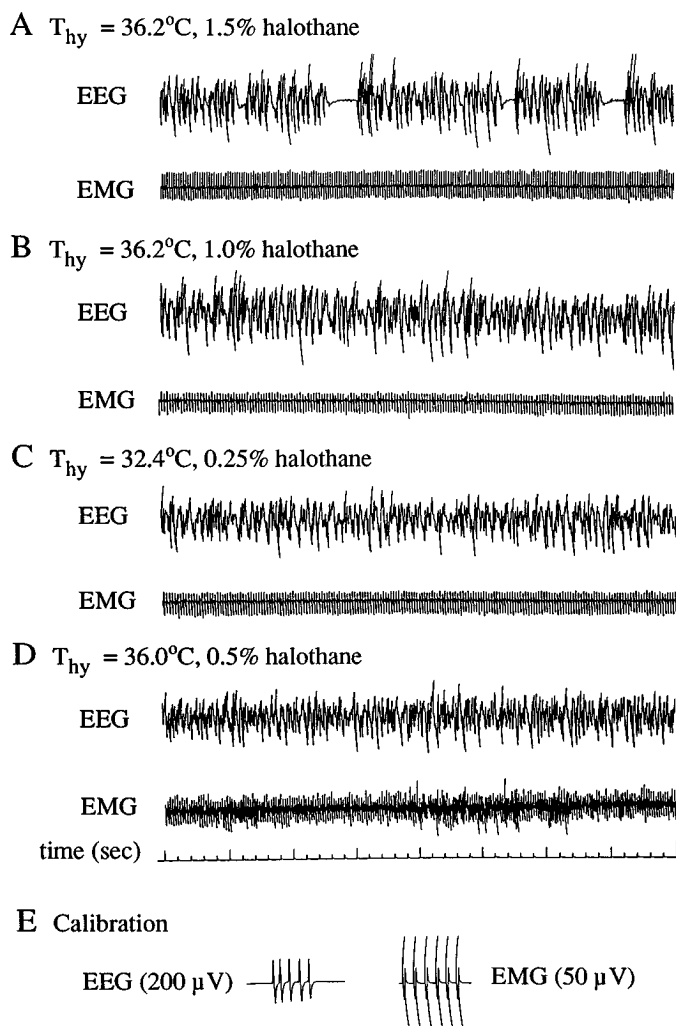


Fig. 1. Recordings of EEG and EMG patterns during halothane anesthesia. EEG and EMG patterns provide useful feedback information for maintaining a constant depth of anesthesia. In this study, concentration of halothane was continuously adjusted to maintain a constant anesthetic effect based on animal's EEG/EMG profile. Target EEG/EMG profile during anesthesia was a high-amplitude EEG pattern [slow-wave-sleep (SWS)-like] and an ECG-dominated EMG pattern. Each of four panels illustrates a 40-s recording of EEG (*top*) and EMG (*bottom*) activity from same animal at different combinations of hypothalamic temperature (T_{hy}) and anesthetic concentration. *A*: normothermic core temperature with excessive anesthesia. Burst-suppression EEG pattern (brief periods of electrical silence interspersed in a SWS-like pattern) signaled that anesthetic dose was too high for desired anesthetic effect. *B*: normothermic core temperature with appropriate anesthesia. Note SWS-like EEG pattern and absence of tonic EMG activity. *C*: hypothermic core temperature with appropriate anesthesia. Note low anesthetic concentration sufficient to maintain target EEG/EMG profile in this condition. *D*: normothermic core temperature with insufficient anesthesia. Increased EMG tone occurred because anesthetic dose was too low. This level of increase in EMG activity did not result in any behavioral movement by animal. *E*: calibration for EEG and EMG.

to behavioral recovery; and 3) postrecovery: the subsequent recording period (see Fig. 2). T_{hy} , EMG activity, and O_2 consumption values for animals in each treatment group during the recovery and postrecovery periods were compared. Because the recovery period was brief and there were no significant changes in the measured variables after emergence from anesthesia in the normothermic and rewarmed

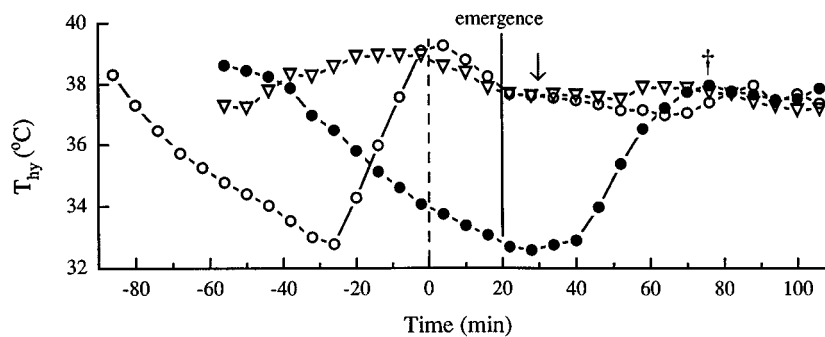


Fig. 2. Example of T_{hy} recorded from 1 representative animal during halothane anesthesia and recovery from anesthesia under 3 thermal regimes used. Time is referenced to termination of anesthesia (vertical dotted line). ●, Hypothermia: animal was anesthetized for 1 h and allowed to recover in a 22–24°C environment. Note decline in T_{hy} extended beyond termination of anesthesia. ▽, Normothermia: T_{hy} was maintained at 37–39°C throughout anesthesia and returned to a 22–24°C environment at *time 0*. ○, Rewarmed: animal was placed in a 22–24°C environment for 1 h of anesthesia, then T_{hy} was raised to 38.7°C, anesthesia was terminated, and animal was returned to a 22–24°C environment. Emergence (vertical solid line): emergence from anesthesia as determined by EEG/EMG criteria (see text for details). Behavioral recovery from anesthesia as determined by initiation of coordinated motor activity: †, normothermic and rewarmed; ‡, hypothermic.

treatment groups, the recovery period was arbitrarily set to 20 min in these groups for comparing the group data. These data were also subjected to a repeated-measures analysis of variance and the Scheffé's method for testing for differences between pairs of means.

RESULTS

Core temperature at the termination of anesthesia had a profound effect on the duration of the recovery process (Table 1). T_{hy} of the hypothermia-treated animals was significantly lower than T_{hy} of the normothermic and rewarmed-treated animals at the termination of anesthesia and at emergence from anesthesia (as determined by changes in the EEG/EMG profiles) but

was not different from the other groups at behavioral recovery (as determined by the initiation of coordinated activity). There were no differences in the time from termination of anesthesia to emergence from anesthesia among the three treatment groups. However, the time from emergence from anesthesia to behavioral recovery was significantly longer in the hypothermic-treatment group than in the normothermic- or rewarmed-treatment groups. The increase in time from emergence from anesthesia to behavioral recovery accounted for the nearly threefold increase in the duration of the total recovery process (from termination of anesthesia to behavioral recovery) in the hypothermic animals.

T_{hy} during emergence from anesthesia was an accurate predictor of the occurrence of postanesthetic tremors (Fig. 3). All eight animals exhibited postanesthetic tremors when anesthetized without supplementary heat application (Fig. 3, left). The duration of tremor activity was 52.1 ± 7.1 (SE) min ($n = 8$), persisting until T_{hy} reached the normothermic range. The hypothermia-treated animals displayed no sustained coordinated motor activity until the tremors subsided. In contrast, in both of the warmed conditions when T_{hy} was $>36^\circ\text{C}$ when the animals emerged from anesthesia, no tremors occurred in the postanesthetic period (Fig. 3, right). Seven of the eight animals maintained at normothermia during anesthesia showed no postanesthetic tremors and regained coordinated motor activity within 10 min after EEG/EMG-defined emergence from anesthesia. However, in one normothermic case, T_{hy} inadvertently dropped to $<35^\circ\text{C}$ between termination of anesthesia and emergence from anesthesia, and that animal exhibited postanesthetic tremors. When T_{hy} was $>36^\circ\text{C}$ during the emergence from anesthesia, all subsequent increases in EMG activity were associated with coordinated movements, not tremors.

EMG activity of the hypothermic-treatment group during the recovery period (from emergence from anesthesia to behavioral recovery) was significantly higher than the EMG activities of the rewarmed- and normo-

Table 1. A comparison of core temperatures at, and the duration of intervals between, transitional events during recovery from halothane anesthesia in rats maintained under various thermal regimes

	Treatment Group		
	Hypothermic	Rewarmed	Normothermic
<i>T_{hy} during recovery, °C</i>			
Termination of anesthesia	32.4 ± 0.2*	38.0 ± 0.2	38.3 ± 0.2
Emergence from anesthesia	32.0 ± 0.3*	37.2 ± 0.4	37.6 ± 0.2
Behavioral recovery	36.7 ± 0.3	37.2 ± 0.3	37.5 ± 0.2
<i>Phases of recovery, min</i>			
Termination to emergence	17.3 ± 2.3	18.4 ± 2.8	18.2 ± 2.3
Emergence to behavioral recovery	54.4 ± 6.0*	7.5 ± 1.4	10.1 ± 1.9
Termination to behavioral recovery	71.8 ± 7.1*	25.9 ± 2.8	28.3 ± 1.5

Values are means ± SE; $n = 8$ rats for all treatment groups. Hypothermic-treatment group animals were maintained in a 23°C environment during 1 h of anesthesia. Normothermic-treatment group animals were actively maintained at hypothalamic temperature (T_{hy}) = 37–39°C throughout 1 h of anesthesia. Rewarmed-treatment group animals were placed in a 23°C environment during 1st hour of anesthesia but were rewarmed to T_{hy} 37–39°C before termination of anesthesia. Emergence from anesthesia was based on changes in EEG/EMG parameters. Behavioral recovery was based on visual determinations: animals arose from a prone position and initiated coordinated motor activities. *Significantly different from other treatment groups ($P < 0.0001$).

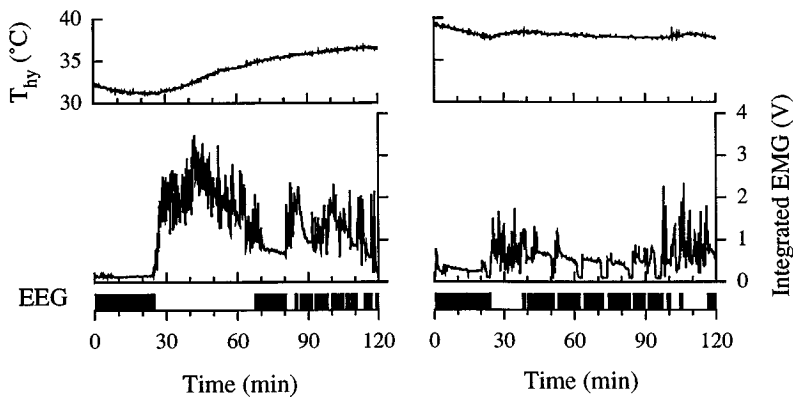


Fig. 3. Examples of profiles after termination of anesthetic application in hypothermic (*left*) and normothermic (*right*) conditions: T_{hy} (*top*), integrated EMG activity (*middle*), and EEG state (*bottom*). Anesthetic was terminated at *time 0*. Although animal emerged from anesthesia after ~ 25 min in both regimes [EEG transformed from SWS-like (solid bar) to waking (W)-like (open)], hypothermic animal experienced a prolonged period of tremors (indicated by high integrated EMG levels) before regaining normothermia and behavioral recovery. Note: combination of a W-like EEG pattern and a suppressed EMG, as expressed by normothermic treatment animal at times 63–65, 72–75, and 84–86 min, is indicative of rapid-eye-movement sleep.

thermic-treatment groups during the recovery period (1.1 ± 0.2 vs. 0.5 ± 0.2 and 0.4 ± 0.1 V, respectively, $P < 0.01$) (Fig. 4A). Although the integrated EMG values alone could not differentiate between tremor activity and coordinated movement by the animals, EMG activity of the hypothermic-treatment group was also significantly higher during the recovery period (when tremors occurred) compared with the postrecovery period (1.1 ± 0.2 vs. 0.6 ± 0.1 V, $P < 0.01$). Increased O_2 consumption accompanied postanesthetic tremors. During the recovery period, O_2 consumption was significantly higher in the hypothermia-treated group than in the normothermia- and rewarmed-treated groups (32.2 ± 6.7 vs. 22.4 ± 4.6 and 19.7 ± 4.9 ml $O_2 \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, respectively, $P < 0.01$) (Fig. 4B). There was no difference in O_2

consumption during the postrecovery period among the three treatment groups.

Behaviorally, when T_{hy} was within the normothermic range on emergence from anesthesia, coordinated movements were initiated within 10 min of emergence. Conversely, the hypothermic animals displayed no coordinated movements until T_{hy} had warmed up to $>36^\circ\text{C}$ and the tremors subsided. Although neither T_{hy} nor tremor activity was a criterion for determining behavioral recovery, behavioral recovery from anesthesia coincided with the cessation of tremor activity and the plateau in T_{hy} in the hypothermia-treated animals. There was a significant difference in the time between emergence from anesthesia and the initiation of coordinated activity between the hypothermic treatment and the rewarmed and normothermic treatments (Table 1 and Fig. 5).

Extension of the duration of the anesthesia to 4 h ($n = 4$) had no effect on the relationship between T_{hy} and postanesthetic tremors: when rewarmed before termination of anesthesia, these animals experienced no tremors on emergence, although the same animals exhibited robust tremors if not rewarmed (data not shown).

DISCUSSION

These results confirm in a nonhuman species that postanesthetic tremors are thermogenic events (3, 23)

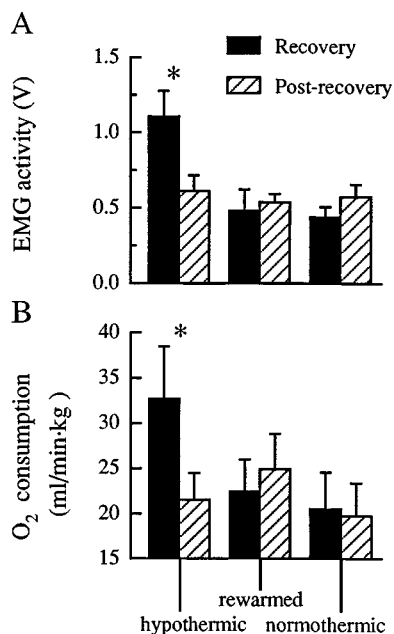


Fig. 4. Postanesthetic EMG activity and metabolic rate are related to thermal status at time of emergence from anesthesia. Integrated EMG activity (A) and O_2 consumption (B) during recovery and postrecovery periods (means \pm SE, $n = 8$). Hypothermic: $T_{hy} < 34^\circ\text{C}$ at termination of anesthesia. Rewarmed: T_{hy} fell to $32\text{--}34^\circ\text{C}$ during anesthesia but was rewarmed to $38^\circ\text{C} < T_{hy} < 39^\circ\text{C}$ before termination of anesthesia. Normothermic: T_{hy} maintained at $37\text{--}39^\circ\text{C}$ throughout anesthesia. *Significantly different from all other groups ($P < 0.01$).

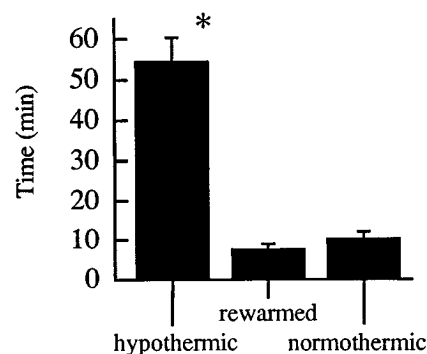


Fig. 5. Warming reduces time between emergence from halothane anesthesia and initiation of coordinated motor activity (bars represent means \pm SE, $n = 8$). Emergence (*time 0*) was determined by EEG and EMG activity criteria; see METHODS. Thermal conditions as described in Fig. 4. *Significantly different from other groups ($P < 0.0001$).

and demonstrate that it is core temperature at the time of emergence from anesthesia, not core temperature during anesthesia, that is correlated with the occurrence of postanesthetic tremors. When T_{hy} was $<36^{\circ}\text{C}$ on emergence from anesthesia, tremors occurred and persisted until T_{hy} returned to normothermy. However, if T_{hy} was within the normothermic range at the time of emergence from anesthesia, postanesthetic tremors did not occur. These results suggest that regardless of the thermal condition during prolonged anesthesia, postanesthetic tremors can be prevented if critical core temperature values are brought to thermal neutrality before emergence from anesthesia.

An important consideration in determining a relationship between temperature and thermoregulatory responses is the site at which temperature is being measured. There has been considerable controversy as to whether postanesthetic tremors were thermogenic events. Skin temperatures and even those of certain areas in the body core (e.g., the esophagus and stomach) can be transiently increased or decreased without eliciting thermoregulatory responses. For instance, the application of heat to the skin does not necessarily decrease peripheral vasoconstriction in hypothermic individuals (9). Thus a local temperature, if measured from a noncritical site, may not be a good predictor for the occurrence of a specific thermoregulatory response. In contrast, it is known that T_{hy} provides a potent input to the thermoregulatory control system (14). Local manipulations of T_{hy} activate appropriate thermoregulatory effector mechanisms, i.e., increases in T_{hy} elicit thermolytic responses (e.g., panting) and peripheral vasodilation, whereas decreases in T_{hy} elicit thermogenic responses (e.g., shivering) and peripheral vasoconstriction (1, 10, 12, 14). Conversely, if local T_{hy} is maintained within normothermy, changes in skin and/or core temperatures have little effect on thermoregulatory output (1, 12, 14). In these studies, T_{hy} served as a measure of core temperature and was an accurate predictor of postanesthetic tremors. However, as a general procedure, measuring T_{hy} during anesthesia is impractical. Alternatively, tympanic membrane temperature, which is readily accessible, can provide a means of accurately assessing the thermal condition of critical thermoregulatory input centers. Although not a direct measure of deep brain temperature, the tympanic membrane is located in close proximity to the brain stem and is isolated from temperature influences of respiratory air currents. Thus, during anesthesia, when vasomotor control is suppressed, changes in tympanic membrane temperature should accurately reflect changes in deep brain temperature. If a relationship between tympanic membrane temperature and thermogenic responses during recovery from anesthesia can be established, tympanic membrane temperature could serve as an acceptable alternative to T_{hy} for monitoring critical core temperatures during, and subsequent to, anesthesia.

The combination of the EEG and EMG signals provided a reliable and easy to interpret feedback signal

for maintaining a constant anesthetic effect in the rats subjected to varying thermal regimes. It has been well documented that anesthetic agents affect the EEG in a dose-dependent manner; however, there is considerable controversy as to the clinical relevance of this relationship (26). When EEG measurements and movement responses to noxious stimuli were compared at varying doses of isoflurane anesthesia, no consistent correlation was observed. At clinically relevant anesthetic concentrations (1.0–1.7% isoflurane), there was a dose-dependent increase in the burst-suppression ratio (%time the EEG was quiescent/recording epoch) and a decrease in the proportion of movement responses to noxious stimulus application, but the responding and nonresponding animals could not be discriminated based on EEG parameters (20). Although EEG alone may not be a useful feedback signal for the maintenance of surgical levels of anesthesia, a combination of EEG and EMG signals can provide useful information for assessing anesthetic effect when it is desirable to maintain an individual in a nonresponsive state with a minimum dose of anesthesia.

Mammals rely on both behavioral and autonomic responses to maintain relatively constant internal temperatures (14). When an individual cannot behaviorally thermoregulate, it must rely on autonomic mechanisms to defend against warm or cold challenges. Peripheral vasoconstriction and thermogenesis are the primary autonomic mechanisms by which mammals combat cold challenges (14). In an unanesthetized individual, decreases in ambient temperature can elicit peripheral vasoconstriction to prevent a drop in core temperature. However, when a thermal challenge exceeds the vasoconstrictive capacity to conserve heat within the body core, core temperatures decrease. Even small decreases in core temperature are sufficient to elicit thermogenic responses. Under normal circumstances, both vasoconstrictive and thermogenic responses are necessary to defend against extreme cold challenges.

Normal thermoregulatory capacity is lost during most general anesthesia treatments (22). Both the ability to conserve heat within specific regions of the body and the ability to generate heat are compromised. Administration of most anesthetics causes a decrease in vascular tone and eliminates vasoconstrictive responses to peripheral cold challenges (22). This results in a net flux of heat from the body core to peripheral tissues and a decrease in core temperature at the onset of anesthesia. If sufficiently challenged, an anesthetized animal can thermoregulate, but the magnitude of the stimulus necessary to elicit a given thermoregulatory response is much greater than that for an unanesthetized animal (27). At low anesthetic levels, peripheral vasoconstriction and shivering thermogenesis can be elicited by decreases in core temperatures (22). Peripheral vasoconstriction is a first-level defense against cold challenges and can be elicited at a higher core temperature than can shivering thermogenesis, even during anesthesia. However, vasoconstriction during anesthesia has little effect on core temperature

because vasoconstriction, although once elicited is effective in preventing further core hypothermia, does not generate heat. Without an accompanying thermogenic response, a vasoconstricted anesthetized individual will remain hypothermic.

If normothermy is maintained throughout anesthesia, the adverse effects associated with postanesthetic hypothermia can be dramatically reduced. However, maintenance of an individual's core temperature above the lower limit of the normothermic range throughout anesthesia does not ensure that thermogenic responses will be eliminated in the postanesthesia recovery period because even within the normothermic range there is considerable variability in the set-point temperature about which an individual regulates its core temperature. Daily core temperature fluctuations of 1.5–2°C are common in mammals, with peak temperatures associated with the active period and the temperature nadirs associated with the rest phase. Other factors that influence the regulated core temperature include vigilance state, previous thermal history, activity level, age, weight, metabolic rate, time of year, and the presence of pyrogens. Thus, even when core temperature is within the normothermic range on emergence from anesthesia, it may be below the desired thermoregulatory set-point temperature, and thermogenic responses will ensue during postanesthetic recovery (18).

Hypothermia is a thermal debt that must be replenished before an individual emerging from anesthesia can resume normal function. Thermogenic shivering is the major physiological mechanism that restores heat to the body core. If postanesthetic tremors represent shivering thermogenesis, then elimination of these tremors would decrease the ability to restore heat to the body core. Pharmacological and physiological manipulations (e.g., muscle relaxants or radiant heat applications to the facial skin) that decrease postsurgical shivering may actually impede rewarming and, thus, may indirectly serve to increase the time required to restore normal function after anesthesia (4, 10, 24). Rather than suppressing the thermogenic effector mechanisms during recovery from anesthesia, it may be more appropriate to decrease the thermoregulatory drive that elicits the thermogenic responses as the individual emerges from anesthesia. If core temperature is at or above the individual animal's regulated set point on emergence from anesthesia, postanesthetic tremors do not occur. In small animals with large surface-to-volume ratios, it is not difficult to heat the body core in a timely manner. In larger animals with lower surface-to-volume ratios, the challenge is to develop means to rapidly bring core temperatures to normothermia during emergence from anesthesia.

The critical inputs from Dr. Paul Franken and Grace Hagiwara during preparation of this manuscript are greatly appreciated. This research was partially supported by a grant from the Upjohn Company.

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Received 12 April 1996; accepted in final form 6 August 1996.

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