Mild Core Hyperthermia Does Not Alter Electroencephalographic Responses during Epidural-Enflurane Anesthesia in Humans

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Study Objectives: To determine the electroencephalographic (EEG) changes induced by mild hyperthermia during enflurane anesthesia and to test the reliability of two new infrared thermometers.

Design: Prospective laboratory evaluation.

Setting: The Thermoregulation Research Laboratory at the University of California, San Francisco.

Volunteers: 6 healthy female volunteers aged 30 ± 8 years.

Interventions: Epidural anesthesia (≈T₅₆ dermatome) was induced and maintained using 2-chloroprocaine anesthesia. General anesthesia was induced by inhalation of nitrous oxide and enflurane and maintained with enflurane at an end-tidal concentration of 1.7%. A minimum of 2°C core hyperthermia was induced by active cutaneous warming, and the volunteers subsequently were passively cooled.

Measurements and Main Results: EEG data were recorded from gold cup electrodes positioned at FP1 and FP2, with the reference electrode at CZ and the ground lead on the mastoid. In addition to routine EEG parameters, we evaluated the bispectral index. Bispectral analysis quantifies the phase coupling between various frequencies in the power spectrum and may be a useful measure of anesthetic depth. Core temperature was measured at the left tympanic membrane and distal esophagus. Core temperature also was determined from the right ear using two new, infrared tympanic membrane thermometers. One of these directly measures tympanic temperature, and the other extrapolates core temperature from the external ear canal. Induction of 2°C core hyperthermia did not produce statistically significant or clinically important changes in beta or delta power, the 95% spectral edge frequency, or the bispectral index. Temperatures recorded from the right ear by the direct thermometer were 0.27°C ± 0.33°C less than those measured in the left ear, but the values correlated well (r² = 0.95 ± 0.04). Temperatures recorded from the right ear by the core temperature extrapolator were 0.42°C ± 0.33°C lower than those measured in the left ear, and the correlation between values was slightly worse (r² = 0.83 ± 0.16).

Conclusions: Since mild core hyperthermia does not alter routine EEG parameters or the bispectral index, typical peri-anesthetic thermal disturbances are unlikely to obscure EEG estimates of anesthetic depth. Both the direct thermometer and the core temperature extrapolator were found to be sufficiently accurate and precise for routine clinical use, but the direct thermometer would be preferable in the peri-anesthetic period.
Keywords: Anesthetics, volatile—enflurane; complications—back pain; electroencephalography; hyperthermia; temperature—measurement techniques, infrared thermography.

Introduction

Mild perioperative hyperthermia is less common than hypothermia. Nonetheless, hyperthermia routinely occurs in patients with infectious fever, blood in the fourth ventricle, or malignant hyperthermia and in patients who are excessively heated or given mismatched blood transfusions. Electroencephalography (EEG) is a popular method of evaluating anesthetic depth and cerebral ischemia. Bispectral EEG analysis is a new, computationally intensive technique that may be more useful than other EEG parameters.

Although the effects of mild hypothermia (e.g., core temperature of 33°C to 36°C) on EEG responses have been described, the EEG effects of mild hyperthermia (e.g., temperature of 38°C to 40°C) during general anesthesia remain unknown. Accordingly, we evaluated the effects of core hyperthermia on EEG parameters, including the bispectral index, during enflurane anesthesia.

Because our protocol required induced hyperthermia, we took this opportunity to evaluate the reliability of two new, portable infrared aural thermometers. The Ototemp 3000 (Exergen Corp., Newton, MA) measures direct, uncorrected tympanic temperature and is designed to provide an accurate measure of core temperature. The Light Touch (Exergen Corp.) estimates core temperature from measured outer ear canal and ambient temperatures and is designed to noninvasively provide an estimate of core temperature with an accuracy comparable to that provided by rectal or oral measurements.

Materials and Methods

With approval from the Committee on Human Research at the University of California, San Francisco, we studied six female volunteers participating in a separate thermoregulatory study. They had the following morphometric characteristics: age, 30 ± 8 years; height, 167 ± 8 cm; weight, 65 ± 13 kg. None was obese or taking medication other than hormonal contraceptives. Women not using hormonal contraceptives were studied during the first 10 days of their monthly cycles. As part of the thermoregulatory investigation, core hyperthermia was induced during combined epidural-enflurane anesthesia.

Treatment Protocol

Studies started at approximately 8:30 A.M. Volunteers fasted during the 8 preceding hours. To minimize anesthetic-induced redistribution hypothermia, a forced-air warming cover (Model 525, Augustine Medical, Inc., Eden Prairie, MN) was positioned over the legs and up to the T10 dermatome. The cover was connected to a Bair Hugger forced-air warmer (Model 200, Augustine Medical, Inc.), which was set on medium (≈40°C) while study monitors were being attached.

An epidural catheter was inserted via the L3–L4 interspace using a standard technique and injected with a test dose (3 ml) of 1.5% 2-chloroprocaine with epinephrine 1:100,000. A 17 ml bolus dose of 1.5% 2-chloroprocaine without epinephrine was slowly administered 5 minutes later, and the catheter was subsequently infused with the same solution at 12 to 15 ml/hr to maintain anesthesia for the duration of the study.

General anesthesia was induced without any premedication by inhalation of 3% to 4% enflurane and 70% nitrous oxide (N2O) in oxygen (O2). Thiopental sodium and opioids were not administered. Vecuronium bromide 0.1 mg/kg was administered intravenously (IV) to facilitate endotracheal intubation and subsequently was infused at a rate sufficient to maintain paralysis. N2O–O2 was discontinued after induction, and the trachea of each volunteer was intubated. Mechanical ventilation was adjusted to maintain end-tidal partial pressure of carbon dioxide (PETCO2) near 35 mmHg. Airway humidification was provided by placing a heat-and-moisture exchanging filter ( Pall Biomedical Products, Glen Cove, NY) between the Y-piece of the circle system and the endotracheal tube.

Anesthesia was maintained with enflurane at an end-tidal concentration of 1.7% in O2, using a Modulus CD integrated anesthesia system (Ohmeda, Inc., Madison, WI). Respiratory gas concentrations were quantified using a calibrated end-tidal gas analyzer (Datex Instrumentarium, Helsinki, Finland).

Core hyperthermia was induced by increasing the setting on the Bair Hugger forced-air warmer to high (≈43°C) while maintaining the temperature of the circulating water blanket at 42°C. Active warming was restricted to the insensate lower body and continued until tympanic membrane temperature was 0.5°C above the temperature causing maximal upper body sweating or until tympanic membrane temperature exceeded 41°C. Volunteers were subsequently slowly cooled by turning off the Bair Hugger, removing the disposable cover from the legs, and decreasing the circulating water temperature to 35°C. Cooling was continued until the core temperature returned to the control value or until 8 hours of enflurane anesthesia had elapsed.

To avoid the potential effects of dehydration, we infused lactated Ringer's solution warmed to 40°C into an antecubital vein on the right arm at a rate of 5 ml/kg/hr until sweating started. The infusion rate was then increased to 15 to 20 ml/kg/hr for the remainder of the study to prevent dehydration during vigorous sweating.

Measurements

We considered lack of cutaneous cold sensation in response to an alcohol-soaked gauze pad to indicate sensory nerve blockade. The dermatomal block level produced by epidural anesthesia was evaluated before induction of and after emergence from enflurane anesthesia.

EEG data were recorded continuously during each
study. Following preparation of the skin with an abrasive solution (Omni-Prep, D.O. Weaver & Co., Aurora, CO), gold cup electrodes were filled with conductive gel (Conducta-1, Rochester Electro-Medical, Inc., Tampa, FL) and fixed in position with collodion adhesive. They were positioned at FP1 and FP2, with the reference electrode at CZ and the ground lead on the mastoid. A microprocessor-based, four-channel monitor (B500, Aspect Medical Systems, Inc., Framingham, MA) was used to collect EEG data, which were recorded on digital tape for subsequent analysis by Aspect Medical Systems, Inc. The acquisition band width was 0.25 to 30 Hz and the electrode impedance was less than 5,000 ohms. In addition to routine EEG parameters, we evaluated the bispectral index.1,2,8

Core temperature was measured at the left tympanic membrane using Mallinckrodt thermocouples (Mallinckrodt, Inc., Argyle, NY). The aural probe was inserted by volunteers until they felt the thermocouple touch the tympanic membrane. Appropriate placement was confirmed when volunteers easily detected a gentle rubbing of the attached wire. The probe was then securely taped in place and the aural canal occluded with cotton. Core temperature also was recorded from the distal esophagus. We have previously demonstrated that tympanic membrane temperatures correlate well with distal esophageal temperatures during induced hyperthermia.9 Temperatures were recorded from thermocouples connected to two Iso-Thermex 16-channel electronic thermometers (Columbus Instruments International Corp., Columbus, OH) having an accuracy of 0.1°C and a precision of 0.01°C. Accuracy of these thermometers was confirmed by comparison to a mercury-in-glass reference thermometer.

Body temperature also was evaluated at 15-minute intervals during enfurane anesthesia using two new, portable infrared-detecting thermometers. The Ototemp 3000 was activated and its 7.8 mm diameter tip inserted into the aural canal. The device was then gently rotated for 5 seconds while the instrument scanned at 10 Hz for the highest temperature. Some practice with the Ototemp 3000 was required to acquire a sufficiently gentle yet accurate sampling technique. Measurements with the Light Touch were taken by inserting the instrument’s 12 mm diameter probe into the outer ear canal. No practice was required with the Light Touch. During measurements, both instruments were covered with thin, disposable plastic films to keep the infrared sensing window clean and prevent disease transmission.

Anesthetic data were obtained from the Capnomac and Modulus CD system, including \( P_{\text{ETCO}_2} \), end-tidal enfurane concentration, oscillometric blood pressure (BP), and oxygen saturation by pulse oximeter. The data were recorded at 90-second intervals using Idacare version 1.3 (Hermes Systems S.a., Angleur, Belgium), which is Macintosh-based (Apple Computer, Cupertino, CA) patient information management software. Temperatures were recorded at 1- to 5-minute intervals using a modification of a previously described data-acquisition system.10 The two systems operated asynchronously on a Macintosh II fx computer.

Data Analysis

EEG data were evaluated at each 0.5°C change in core temperature, starting with control values recorded shortly after induction of enfurane anesthesia. Values were compared using repeated-measures analysis of variance and Dunnett’s tests for comparison to control. Results are reported as means ± SD. A value of \( p < 0.05 \) was considered statistically significant.

Temperatures obtained from the distal esophagus, the Ototemp 3000, and the Light Touch in each individual were compared with values recorded from the tympanic membrane thermocouple using linear regression. Thus, for the purpose of this analysis, the tympanic membrane temperature recorded from the thermocouple in the left ear was considered the reference value in each individual. The difference between 37°C and the value predicted by the regression equation when the reference value was set to 37°C was considered the offset. The offset and the slope of the regression equations quantify the accuracy of the different temperature measures.

Difference was defined as the absolute value of temperature recorded from the tympanic membrane thermocouple subtracted from the other measurement sites. The average difference was calculated in each individual, and from these averages, we calculated the mean difference for the entire group. Thus, difference is an expression of the reliability of the various temperature-monitoring methods. Reliability of the measurements also is expressed as the regression correlation coefficient (\( r^2 \)).

Results

Epidural anesthesia produced sympathetic blockade ranging from \( T_9 \) to \( T_{11} \). End-tidal enfurane concentration averaged 1.70% ± 0.02% and rarely deviated more than 0.03% from our target of 1.7%. Core temperature typically increased and decreased at about 0.7°C per hour. There were no clinically important or statistically significant changes in mean BP in any volunteer during hyperthermia. In contrast, heart rate increased about 20 beats per minute at the highest temperatures. The sweating threshold (core temperature at which sweating was first observed) was 38.8°C ± 0.4°C.

Induction of 2°C core hyperthermia did not produce statistically significant or clinically important changes in beta or delta power, the 95% spectral edge frequency, or the bispectral index (Figure 1). When values were stratified according to the direction of core temperature change, differences remained trivial. Onset of sweating was not accompanied by detectable EEG alterations.

Distal esophageal temperatures exceeded those recorded from the thermocouple adjacent to the left tympanic membrane by 0.25°C ± 0.07°C. The difference between these temperatures did not increase significantly after sweating started. Temperatures recorded from the right ear by the Ototemp 3000 were 0.27°C ± 0.33°C less than those measured in the left ear, but the values correlated well (\( r^2 = 0.95 ± 0.04 \)). Temperatures recorded from the right ear by the Light Touch were
0.42°C ± 0.33°C less than those measured in the left ear, and the correlation between values was slightly worse ($r^2 = 0.83 ± 0.16$) (Table 1).

One volunteer complained of severe, nonpositional back pain after the epidural anesthesia was discontinued. It was relieved within 1.5 hours by epidural administration of fentanyl 50 μg and IV administration of ketorolac 60 mg. Similar pain was not observed in more than 20 volunteers who participated in preliminary and similar studies. Thus, our current protocol, used in more than 25 volunteers, only once caused back pain similar to that reported previously.19-14

![Figure 1](image)

**Figure 1.** Beta and delta power, the 95% spectral edge frequency (SEF), and the bispectral index (BIS) at normothermia (37.2°C ± 0.5°C; ATemp = temperature zero) and during 2°C of core hyperthermia. A constant end-tidal enflurane concentration of 1.7% was maintained throughout the measurements. Electroencephalographic (EEG) values during increasing and decreasing core temperature are included in the figure. There was no significant direction-dependent difference. Core hyperthermia did not produce statistically significant or clinically important EEG changes.

## Discussion

Mild core hypothermia increases somatosensory and corticmotor evoked potential latencies15 and decreases the onset time of magnetic motor evoked potentials.16 Interestingly, hyperthermia to 42°C markedly decreases somatosensory evoked potential amplitude. Hyperthermia to 35°C only minimally alters EEG patterns during isoflurane anesthesia, but lower temperatures suppress EEG activity.² Our data indicate that up to 2°C of core hyperthermia during enflurane anesthesia has no clinically important influence on EEG responses. Taken together, these data suggest that typical perianesthetic thermal disturbances are unlikely to confound interpretation of EEG responses.

Such insensitivity to core temperature is consistent with the potency of volatile anesthetics being minimally altered by small temperature perturbations. Typically, minimum alveolar concentration is reduced 5% per °C of core hypothermia.17,18 Insensitivity to temperature perturbations also is fortuitous because EEG responses will not require temperature correction when used as monitors of anesthetic depth.

EEG patterns would have differed if we had administered different enflurane doses or different types of anesthesia. We do not have data on the temperature dependence of EEG responses during other types of anesthesia, but it is likely that the well-known differences among types of anesthesia would exceed the differences provoked by typical perioperative perturbations. Core temperatures higher than those tested in this study may significantly alter EEG responses, but such temperatures are unusual. We administered epidural anesthesia in this protocol to prevent cutaneous thermal sensation; it is unlikely that regional anesthesia directly alters EEG responses.

Bispectral analysis not only takes into account the frequency and amplitude of EEG component waves, but it also quantifies the relationships existing between them.7,8 In contrast to power spectral analysis, which assumes all component waves are fundamental frequencies, bispectral analysis can determine whether harmonic frequencies are present. Such harmonics indicate synchronization of the EEG, and their quantification appears to be a useful measure of anesthetic depth.¹

The tympanic membrane temperature in the left ear was, on average, about 0.3°C higher than the uncorrected

### Table 1. Correlation between Infrared Tympanic Membrane and Distal Esophageal Temperatures

<table>
<thead>
<tr>
<th>Offset (°C)</th>
<th>Slope</th>
<th>$r^2$</th>
<th>Difference (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal esophageal</td>
<td>0.25 ± 0.03</td>
<td>0.96</td>
<td>0.99</td>
</tr>
<tr>
<td>Ototemp 3000</td>
<td>-0.27 ± 0.33</td>
<td>1.01</td>
<td>0.95</td>
</tr>
<tr>
<td>Light Touch</td>
<td>-0.49 ± 0.33</td>
<td>0.98</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Note: Distal esophageal temperatures slightly exceeded those recorded from the thermocouple adjacent to the right tympanic membrane. The difference between these temperatures did not increase significantly after sweating started. Temperatures recorded from the right ear by the Ototemp 3000 (Exergen Corp., Newton, MA) were typically about 0.25°C lower than those measured in the left ear; however, the correlation between the two measures was excellent. Temperatures recorded from the right ear by the Light Touch were considerably more variable than those recorded by the Ototemp 3000.

typanic membrane temperature measured by the Ototemp 3000 and about 0.5°C higher than the indirect tympanic temperature measured by the Light Touch. The correlation with the left tympanic membrane temperature and the difference between thermocouple and infrared measurements were excellent for the Ototemp 3000 and moderately worse for the Light Touch. The accuracy and reproducibility of the Ototemp 3000 was largely dependent on user technique, whereas the Light Touch depended more on the anatomy of the external ear. The volunteers preferred the Light Touch because of its rapid and noninvasive technique. These new infrared ear thermometers offer a reliable alternative to current methods of core temperature measurement in the clinical setting.

Some animals have special countercurrent vascular structures in the nose that help maintain a nearly normal brain temperature even when the trunk becomes hyperthermic. Distal esophageal (trunk) and tympanic membrane temperatures in humans may differ slightly during exercise, airway humidification and heating, or facial fanning in a warm environment, a difference proposed to represent specific brain cooling. The extent to which these gradients represent a true core-brain difference or an artifactual decrease only in tympanic membrane temperature remains controversial.

Although our study was not designed to evaluate brain cooling mechanisms, lack of increase in the esophageal-to-tympanic membrane temperature difference suggests that the brain was not specifically cooled during our study conditions. An increase in the gradient during active vasodilation may have been observed had we included facial fanning in the protocol.

Although one volunteer complained of severe, nonpositional back pain after the epidural anesthesia was discontinued, similar pain was not observed in more than 20 other volunteers who have participated in preliminary and similar studies. Thus, our current protocol, used in more than 25 volunteers, only once caused back pain similar to that reported previously.

We and others have reported severe back pain after epidural administration of large volumes of 2-chloroprocaine (Nesacaine-MPF). A likely etiology for the pain is EDTA-mediated hypocalcemic tetany in paraspinal muscles. Despite our previous experience, we chose 2-chloroprocaine for the current study because this drug is rapidly metabolized after absorption into the systemic circulation and thus unlikely to influence EEG processing via this route.

To reduce the possibility of back pain, we made four changes in our administration protocol: (1) the initial bolus dose was given slowly and subsequent drug was administered by infusion to minimize the spread of anesthetic outside the epidural space; (2) instead of Nesacaine-MPF, we used Chloroprocaine HCl, USP without EDTA; (3) we used 1.5% chloroprocaine rather than 3%; (4) the block was maintained at a lower level (≈T10 vs. ≈T3). These manipulations apparently were sufficient because only one volunteer in this study, and none in preliminary and similar studies, experienced back pain typical of that produced by chloroprocaine, a frequency far lower than previously reported.

In summary, mild core hyperthermia does not alter routine EEG parameters or the bispectral index. Thus, typical perianesthetic thermal disturbances are unlikely to obscure EEG estimates of anesthetic depth. Both the Ototemp 3000 and the Light Touch were sufficiently accurate and precise for routine clinical use, but the Ototemp 3000 would be preferable in the perioperative period.

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