

## Isoflurane Anesthesia and Circadian Temperature Cycles in Humans

Daniel I. Sessler, M.D.,\* Kathryn A. Lee, R.N., Ph.D.,† Joseph McGuire, B.S.‡

Cognitive performance in postsurgical patients may be impaired by disturbances of normal circadian rhythm analogous to those produced by rapid transmeridian travel ("jet lag"). We therefore tested the hypothesis that isoflurane anesthesia alone produces a phase-delay in the human circadian temperature rhythm. We monitored central body temperature rhythms (using an ingested sensor) in five young, healthy, male volunteers at 3-min intervals for a total of 5 days. On the 3rd day, 3 h of 1.0% isoflurane anesthesia was administered beginning at  $\approx 10:00$  AM. Thiopental, opioids, and other medications were not administered; volunteers were kept normothermic during anesthesia. Visual inspection of the data confirmed that periodicity of the temperature cycles remained near 24 h and that the curve was sinusoidal. Data were fit using a two-step sine and cosine regression for each 24-h period. Before anesthesia, volunteers demonstrated a consistent 24-h cycle, with a mean temperature (mesor) of  $36.8 \pm 0.2^\circ$  C, amplitude of  $0.8 \pm 0.2^\circ$  C, and time of maximum temperature (acrophase) of  $3:06$  PM  $\pm 2.4$  h. Isoflurane anesthesia did not produce significant changes in the central temperature mesor. Peak-to-trough range (amplitude) of the temperature cycle was significantly reduced on the day of anesthesia ( $0.5 \pm 0.2^\circ$  C) but returned to normal on the subsequent day. Compared with the 2 days preceding isoflurane administration, there was no statistically significant change in acrophase on the day following anesthesia. These data do not support our hypothesis and suggest that the internal timer controlling circadian temperature cycles is resistant to clinical concentrations of isoflurane. (Key words: Temperature, thermoregulation: circadian rhythm; diurnal variation. Sleep.)

COGNITIVE PERFORMANCE in postsurgical patients is frequently impaired for several days, even after minor ambulatory procedures.<sup>1</sup> Possible causes include residual anesthesia, sleep disturbances, surgical pain, and medications administered to treat pain.<sup>2</sup> Impaired cognitive performance is often a manifestation of disturbances of normal circadian rhythm analogous to the syndrome produced by rapid transmeridian travel ("jet lag").<sup>3</sup>

Humans normally manifest an  $\approx 24$ -h cyclical variation in a number of functions including body temperature, secretion of melatonin and growth hormone, sleep, and activity.<sup>3</sup> Previous studies suggest that a circadian phase-delay follows anesthesia and surgery in humans.<sup>4,5</sup> How-

ever, these studies failed to control duration of surgery, type of anesthesia, perioperative hypothermia, incisional pain, and postoperative medications. To determine the effect of anesthesia alone, we tested the hypothesis that isoflurane anesthesia phase-delays circadian temperature rhythms in humans.

### Materials and Methods

With Committee on Human Research approval and informed consent, we measured circadian central body temperature rhythms in five male volunteers before and after isoflurane anesthesia. All had habitual bed times between 10:00 PM and 12:00 AM and drank fewer than three cups of coffee each day. They did not smoke tobacco, and did not take medications during the study period. The study was conducted in San Francisco, between March 1990 and January 1991.

Central temperatures were monitored at 3-min intervals for a total of 5 days using an ingested quartz sensor transmitting to an external antenna and data recorder (CorTemp<sup>®</sup>, Human Technologies, Inc., St. Petersburg, FL); this technique compares well with rectal temperature monitoring.<sup>§</sup> The ingested sensors may not provide reliable readings for the first 1-2 h (while in the stomach), but then do so in the intestines, where they remain for 1-2 days. The external antenna is incorporated into a harness that is worn over the chest and abdomen, and is connected to a data recorder that weighs  $\approx 1$  kg and requires battery replacement at  $\approx 18$ -h intervals. Central temperature rhythms are considered a reliable indicator of endogenous circadian cycles.<sup>6</sup>

After 2 days of baseline temperature measurements, volunteers fasted overnight and were anesthetized starting between 9:30 and 10:30 AM. Anesthesia was induced by inhalation of 3-4% isoflurane and 70% nitrous oxide in oxygen, and tracheas were intubated after muscle relaxation was provided by intravenous vecuronium 0.1 mg/kg. Thiopental, opioids, and other medications were not administered, and no surgery was performed. Anesthesia was maintained with isoflurane ( $\approx 1.0\%$  end-tidal concentration) in a mixture of 1 l/min oxygen and 4 l/min air; end-tidal carbon dioxide tension was maintained near 35 mmHg.

\* Assistant Professor of Anesthesia, Department of Anesthesia.

† Assistant Professor of Nursing, Department of Family Health Care Nursing.

‡ Staff Research Associate, Department of Anesthesia.

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Address reprint requests to Dr. Sessler: Department of Anesthesia, Room C-450, University of California, San Francisco, California 94143-0648.

§ Cutchis PN, Hogrefe AF, Lesho JC: The ingestible thermal monitoring system. Johns Hopkins APL Technical Digest 9:16-21, 1988.

Respiratory gases were administered *via* a partially re-breathing circle system. Airway humidification was provided by placing a heat and moisture exchanger (ThermoFlo Filter<sup>®</sup>, ARC Medical, Inc., Clarkston [Atlanta], GA) between the Y-piece of the circle system and the endotracheal tube. Approximately 1 l of warmed lactated Ringer's solution was administered intravenously during each anesthetic; the rate of fluid administration was varied to maintain systolic blood pressure within 20% of baseline values.

Continuous electrocardiography (ECG) using lead 2 was performed during each anesthetic. Blood pressure was evaluated oscillometrically (Dinamap<sup>®</sup> 1846 SX, Critikon, Inc., Tampa, FL) at 5-min intervals. Hemoglobin oxygen saturation was measured using a Nellcor N200 pulse oximeter (Hayward, CA). Respiratory gas concentrations were quantified using a Datex Capnomac<sup>®</sup> gas analyzer (Datex Medical Instrumentation, Inc., MA). The Capnomac<sup>®</sup> was calibrated using a known mixture of gases before each study.

During anesthesia, central temperatures were maintained near each volunteer's control temperature by adjusting the heater of a Bair Hugger<sup>®</sup> forced-air warmer (Augustine Medical, Inc., Eden Prairie, MN).<sup>7</sup> The warming cover was kept in place throughout the control, anesthetic, and recovery periods. During anesthesia, ambient light was maintained at a typical operating room level; eyes were taped shut, but no further effort was made to prevent light from entering.

After  $\approx 160$  min of anesthesia, the end-tidal isoflurane concentration was increased to  $\approx 2\%$  and the trachea extubated. The end-tidal concentration was then returned to 1.0%, where it was maintained (*via* face mask) until total anesthetic administration time was 3 h. Isoflurane concentration in the fresh gas supply was then reduced to zero, and the volunteer allowed to emerge from anesthesia. Vecuronium neuromuscular blockade was not antagonized, but adequate muscle strength was documented by an intact train-of-four response to peripheral nerve stimulation. Following  $\approx 2$  h of recovery, volunteers were escorted home and were free to resume normal activities.

Transmitted central temperature data were smoothed using a 1-h (20-point) moving average. Visual inspection confirmed that periodicity of the temperature cycles remained near 24 h and that the curve was sinusoidal. Data were fit using a two-step sine and cosine regression for each 24-h period, as previously described.<sup>¶</sup> From the regression and  $\beta$  coefficients, we calculated the mesor (mean central temperature), amplitude (peak-to-trough

temperature range), and acrophase (time of daily temperature range) for the circadian cycle.

Changes in circadian rhythm before and after anesthesia were analyzed using repeated-measures analysis of variance and Dunnett's tests; data from the days immediately preceding anesthetic administration were considered control values. Data are expressed as means  $\pm$  standard deviations; differences were considered statistically significant when  $P < 0.05$ .

## Results

The CorTemp<sup>®</sup> system did not perform well, and we experienced technical failures in many volunteers before acquiring the data reported here. Some sensors were not properly calibrated, and others failed to operate at all. The antenna required frequent manipulation, and on several occasions, data could not be retrieved from the recorder.

The mean age of volunteers was  $26 \pm 2$  yr; weight was  $64 \pm 8$  kg; and height was  $173 \pm 6$  cm. Average end-tidal isoflurane concentration was  $1.0 \pm 0.2\%$ . End-tidal carbon dioxide tension was  $37 \pm 3$  mmHg during isoflurane administration. Blood pressure remained within 20% of control values, and hemoglobin oxygen saturation was  $\geq 97\%$ , during anesthesia.

All volunteers recovered from isoflurane anesthesia quickly and were ready to go home within 2 h after isoflurane administration was discontinued. No complications resulted from the study other than postanesthetic nausea ( $n = 4$ ) and vomiting ( $n = 2$ ). Most volunteers slept for 2–3 h at home the afternoon following isoflurane administration.

Smoothed temperature data and the fitted cosine curve for the first and last volunteers are shown in figures 1 and 2. Before anesthesia, volunteers demonstrated a consistent 24-h cycle, with a mesor of  $36.8 \pm 0.2^\circ\text{C}$ , amplitude of  $0.8 \pm 0.2^\circ\text{C}$ , and acrophase of  $3:06\text{ PM} \pm 2.4\text{ h}$ . There were no significant changes in the mesor during the study. Amplitude of the temperature cycle was significantly reduced on the day of anesthesia ( $0.5 \pm 0.2^\circ\text{C}$ ) but returned to normal on the subsequent day.

Acrophase of the circadian cycle could not be determined in two volunteers on the day of anesthesia because their cycle amplitudes were sufficiently low to preclude adequate regression fit ( $r^2 < 0.35$ ). Consequently, we attempted no statistical analysis of the acrophase data on the day of anesthesia; compared with the average of the 2 (control) days preceding isoflurane administration, there were no statistically significant changes in acrophase on the day after anesthesia: individual phase changes were 1.2, 2.1,  $-0.7$ ,  $-1.6$ , and  $-0.7$  h, averaging  $0.1 \pm 1.5$  h (fig. 3). The two volunteers with the lowest temperature amplitude and most disturbed cycle shape experienced

¶ Lee KA: Circadian temperature rhythms in relation to menstrual cycle phase. *J Biol Rhythms* 3:255–263, 1988.

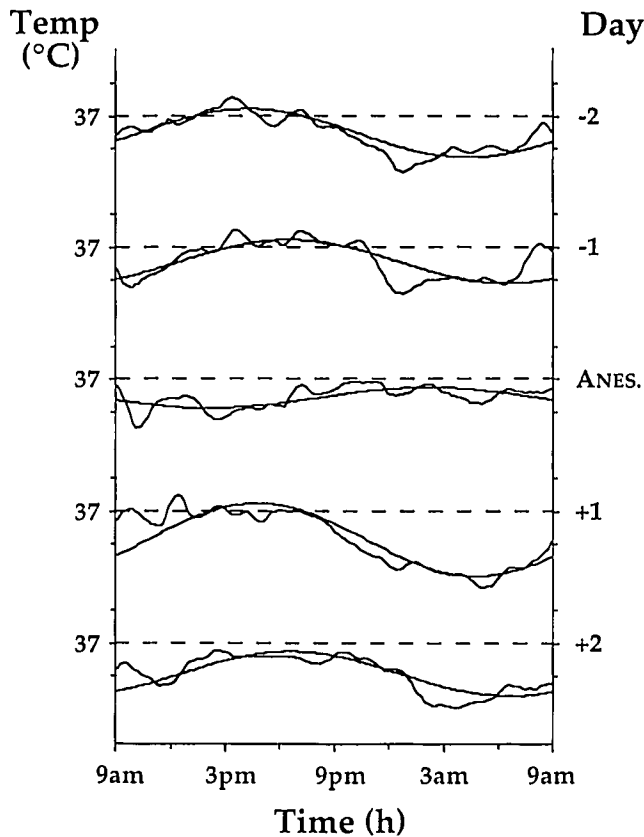


FIG. 1. Smoothed transmitted central temperatures and cosine regression for the first volunteer are indicated in 24-h epochs starting at 9:00 AM. Elapsed days (relative to isoflurane administration) are indicated on the right axis. Central temperatures are indicated on the left axis; each tick mark represents 0.5° C.

considerably more nausea and dysphoria following anesthesia than the other participants.

### Discussion

Biologic synchronization to the natural 24-h light/dark cycle is typical and has been demonstrated in bacterial motility, plant movement, and insect feeding. Circadian variations for more than 100 physiologic variables have been identified in humans. So many biologic responses display daily cycles that some investigators believe non-varying parameters to be an exception, not the rule.<sup>3</sup> Circadian cycles with potential clinical relevance include plasma cortisol and growth hormone, sensitivity to inhaled and intravenous anesthetics and cancer chemotherapeutic drugs, urine volume and potassium excretion, coagulation, hepatic function, and sleep/activity patterns.<sup>8-13,\*\*</sup>

Circadian periodicity is maintained by internal timing mechanisms that serve as biologic "clockworks." These

clockworks have an intrinsic period that is not exactly 24 h (usually near 25 h in humans).<sup>14</sup> The intrinsic period is adjusted to 24 h by "time-givers," or *zeitgebers*, i.e., external time signals, including light/dark period, social cues, and food availability.<sup>15</sup> There are at least two separate timing mechanisms. One is located in the suprachiasmatic nuclei and controls non-rapid-eye-movement (REM) sleep, activity, drinking, and corticosteroid production. The other controls REM sleep, body temperature, and feeding, but its location is unknown.<sup>16,17</sup>

There are three categories of circadian disorders.<sup>3</sup> Periodicity disorders result from inadequate exposure to *zeitgebers*. They occur in some blind individuals, patients in intensive care, and people living North of the Arctic circle (especially before electric lighting was common). Amplitude disorders occur when normal daily cycles are prevented by increased intracranial pressure or destruction of circadian timers (by tumor, stroke, or surgery). Phase disturbances are the most common circadian disorders and often result from rapid transmeridian travel ("jet lag") or shift work. Consequences include delayed sleep, insomnia, emotional disturbances, and cognitive impairment.<sup>18-20</sup> Productivity lost to jet lag probably costs businesses more than a billion dollars each year.<sup>21</sup>

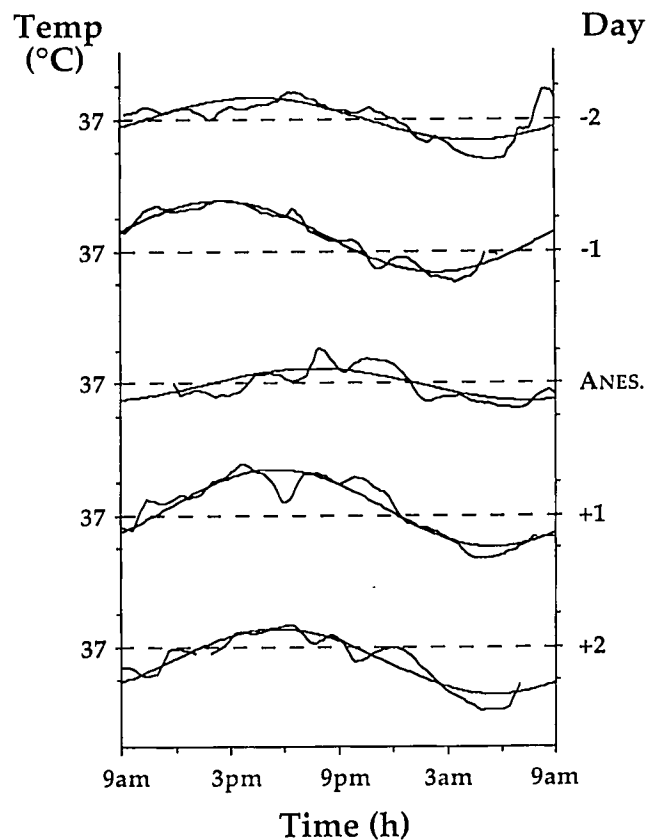


FIG. 2. Central temperatures and cosine regression for the fifth volunteer.

\*\* Parmeggiani PL: Thermoregulation during sleep in mammals. NIPS 5:208-212, 1990.

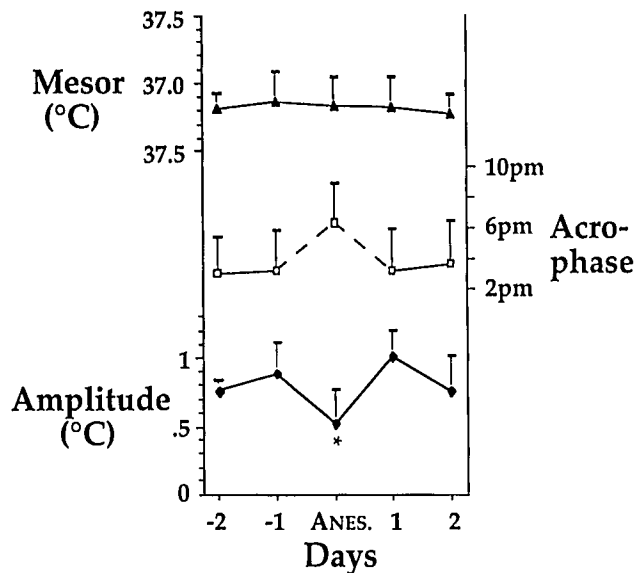


FIG. 3. There were no statistically significant changes in the mean central temperature (mesor). On the 2 days before anesthesia, volunteers demonstrated a consistent 24-h sinusoidal cycle, with a peak-to-trough temperature range (amplitude) of  $0.8 \pm 0.2^\circ\text{C}$ . Amplitude of the temperature cycle was significantly reduced on the day of anesthesia ( $0.5 \pm 0.2^\circ\text{C}$ ) but returned to normal on the subsequent day. Before anesthesia, time of the daily temperature maximum (acrophase) of the circadian cycle was at  $3:06\text{ PM} \pm 2.4\text{ h}$ . Acrophase could not be determined in two volunteers on the day of anesthesia because their cycle amplitudes were sufficiently low to preclude adequate regression fit ( $r^2 < 0.35$ ). Consequently, only acrophase data on the remaining three volunteers are plotted on the day of anesthesia; these data are shown with dashed lines. We attempted no statistical analysis of the acrophase data on the day of anesthesia, but compared with the two days preceding isoflurane administration, there were no statistically significant changes in acrophase on the days following anesthesia.

Previous studies report that circadian temperature cycles are phase-delayed after operations<sup>4,5</sup>; the extent to which such delay results from surgery, stress, other anesthetic drugs, subject selection, pain, or pharmacologic treatment of pain remains unknown. However, the reported delay is unlikely to result only from perianesthetic hypothermia because central circadian timers are known to be temperature-compensated.<sup>22</sup> Similar delay was reported following abdominal surgery in rats anesthetized with ketamine and xylazine.<sup>23</sup>

Our hypothesis was that 3 h of isoflurane anesthesia alone would phase-delay the circadian temperature cycle. A delay matching the duration of anesthesia would have been analogous to west-to-east jet travel across three time zones. (Circadian disruption from eastward travel [phase-advance] is usually worse than that from westward travel because most people have natural phase-delaying cycles with a tendency to exceed 24 h.) Our data do not support this hypothesis, and suggest that the internal timer controlling circadian temperature cycles is resistant to clinical concentrations of isoflurane.

Our volunteers returned to their routine environment after anesthesia. However, even in a constant environment, recovery from a phase change usually requires about 1 day for each 60–90 min of shift.<sup>24,25</sup> It is thus unlikely that the acrophase was significantly shifted by isoflurane but returned to normal by the following day. Although we did not identify a statistically significant phase delay following isoflurane anesthesia, inherent variability in the acrophase was comparable to the expected delay. Consequently, an impractically large number of volunteers would be required to prove that no delay occurred. Nonetheless, our data suggest that 3 h of isoflurane anesthesia *per se* does not produce a consistent circadian phase delay.

Studies in animals indicate that circadian phases are disturbed by a variety of anesthetic and other drugs, including theophylline, caffeine, ethanol, pentobarbital, L-dopa, and dexamethasone.<sup>26</sup> Frequently, a given medication produces a phase-delay when administered at one time but produces a phase-advance when given at another time.<sup>26</sup> Although no acrophase change was observed in our volunteers, who were anesthetized midmorning, it remains possible that isoflurane administered at a different time of day would alter the circadian temperature cycle. However, it is unlikely that isoflurane produces large phase changes when administered during the hours most surgery is performed.

Temperature was the only peripheral manifestation of internal periodicity we tested. It remains possible that the phase of another internal timer was altered. Normally, all internal clocks are similarly synchronized by *zeitbegers* to 24 h. However, when external time cues are inadequate or conflict, the timers can become internally desynchronized (displaying cycles with differing periods). Physiologic consequences of internal desynchronization may include substantial inhibition of thermoregulatory responses as well as impairment in cognitive performance.<sup>27,28</sup>

Amplitude of the circadian temperature cycle was reduced on the day of anesthesia and returned to normal the subsequent day. It is unlikely that this minor fluctuation is of any clinical significance.

In summary, 3 h of isoflurane anesthesia in nonsurgical volunteers reduced amplitude of the circadian temperature rhythm on the day of anesthesia but did not statistically significantly alter the cycle acrophase. Other factors, including pain, medications, and sleep disturbance, may explain previously observed postoperative cognitive impairment.

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