Anesthesiology
1998; 89:648–56
© 1998 American Society of Anesthesiologists, Inc.
Lippincott Williams & Wilkins

Paralysis Only Slightly Reduces the Febrile Response to Interleukin-2 during Isoflurane Anesthesia

Rainer Lenhardt, M.D., Chiharu Negishi, M.D.,† Daniel I. Sessler, M.D.,‡ Makoto Ozaki, M.D.,§ Farzin Tayefeh, M.D.,† Andrea Kurz, M.D.‖*

Background: **Fever sometimes occurs during anesthesia. However, it is rare considering how often pyrogenic causes are likely to be present and how common fever is after surgery. This low incidence results in part from dose-dependent inhibition of fever by volatile anesthetics. Paralysis, however, may contribute by preventing shivering and the associated increase in metabolic heat production. Therefore the authors tested the hypothesis that paralysis during anesthesia decreases the febrile response to pyrogen administration.**

Methods: **Seven volunteers each participated on two study days. They were given 30 IU/g intravenous interleukin-2, followed 90 min later by an additional 70 IU/g dose. Anesthesia was induced 30 min after the second dose and maintained for 6 h with 0.6 minimum alveolar concentration isoflurane. The volunteers were randomly assigned to (1) paralysis with vecuronium or (2) no muscle relaxants. Body heat content and distribution were determined from measured tissue and skin temperatures. Data are presented as mean ± SD; $P < 0.05$ was considered significant.**

Results: **There was no clinically important difference in peak core (tympanic membrane) temperatures on the unparalyzed (37.6 ± 0.9°C) and paralyzed (37.2 ± 0.6°C) days. Core heat content increased 1.2 ± 0.7 kcal/kg over the last 5 h of anesthesia on the unparalyzed day, but only by 0.9 ± 0.4 kcal/kg when the volunteers were paralyzed. Peripheral tissue heat content increased 0.1 ± 1.1 kcal/kg on the unparalyzed day but decreased 1.1 ± 0.7 kcal/kg when the volunteers were paralyzed. Consequently, body heat content increased 1.3 ± 1.3 kcal/kg on the unparalyzed day but decreased significantly by 0.2 ± 0.8 kcal/kg when the volunteers were paralyzed.**

Conclusions: **Paralysis prevented shivering from increasing the metabolic rate. Consequently, body heat content decreased during paralysis, whereas otherwise it increased. Thermoregulatory vasoconstriction was nonetheless able to maintain similar peak and integrated core temperatures on each study day. Administration of muscle relaxants thus is not the primary explanation for the relative paucity of intraoperative fever. (Key words: Fever; hyperthermia; muscle relaxant; pyrogen; temperature; thermoregulation.)**

* Research Fellow, Department of Anesthesia and Perioperative Care, University of California, San Francisco; Assistant Director, Outcomes Research™, Department of Anesthesia and General Intensive Care, University of Vienna.

† Research Fellow, Department of Anesthesia and Perioperative Care, University of California, San Francisco.

‡ Professor, Department of Anesthesia and Perioperative Care, University of California, San Francisco; Professor, Ludwig Boltzmann Institute for Clinical Anesthesia and Intensive Care; Director, Outcomes Research™, and Vice-Chair, Department of Anesthesia and General Intensive Care, University of Vienna.

§ Associate Professor, Department of Anesthesia and Perioperative Care, Tokyo Women's Medical College, Tokyo, Japan.

‖Associate Director, Outcomes Research™, and Professor, Department of Anesthesia and General Intensive Care, University of Vienna.

Received from the University of California, San Francisco; University of Vienna; and Tokyo Women's Medical College. Submitted for publication January 15, 1998. Accepted for publication May 6, 1998. Supported by NIH Grant GM49670, the Joseph Drown Foundation (Los Angeles, CA), the Fonds zur Förderung der Wissenschaftlichen Forschung (Vienna, Austria), the Austrian National Bank Foundation, and the Max Kade Foundation (New York, NY). Major corporate funding for the Outcomes Research Laboratory is provided by Augustine Medical, Inc. and Scott Laboratories, Ltd. The authors do not consult for, accept honoraria from, or own stock or stock options in any anesthesia-related company.

Address reprint requests to Dr. Sessler: Department of Anesthesia, Box 0648, University of California, San Francisco School of Medicine, 374 Parnassus Avenue, Third floor, San Francisco, California 94143. Address electronic mail to: sessler@vaxine.ucsf.edu

UNLIKE normal thermoregulatory control, which is largely neuronally mediated,[1,2] fever is activated by circulating pyrogens. The major pyrogenic cytokines appear to be interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF), and interferon alpha.[3–6] Other factors also contribute.[7]

The mechanisms by which pyrogens activate hypothalamic control centers remain controversial,[8,9] but there is considerable evidence that vagal afferents are involved.[10] Fever synchronously augments thermoregulatory response thresholds, which can be considered an increase in the "set point" (the target body temperature). Core temperature elevation then results from activation of cold defenses, including vasoconstriction and shivering.[11]

Intraoperative fever is relatively rare considering how often pyrogenic causes are likely to be present during surgery and how common fever is after operation. One

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-19980900-00014.pdf by guest on 20 April 2024

factor that surely contributes to the low incidence of intraoperative fever is direct, presumably central, inhibition of the febrile response by volatile anesthesia.[12] Intraoperative fever may also be rare because many surgical patients are given muscle relaxants. Paralysis, of course, prevents shivering and the associated increase in metabolic heat production, leaving the development of fever entirely dependent on thermoregulatory vasoconstriction. Alteration in vasomotor tone is one of the primary factors that influence perioperative core temperature.[13–15] However, the extent to which vasoconstriction alone can sustain fever during anesthesia remains unknown.

Accordingly, we tested the hypothesis that neuromuscular block during anesthesia decreases the febrile response to pyrogen administration. To independently evaluate the contributions of shivering and vasoconstriction to fever, we simultaneously measured body heat content and the regional distribution of tissue heat. Finally, we measured plasma cytokine concentrations to further refine our human volunteer fever model.[12]

Methods

With approval from the Committee on Human Research at the University of California, San Francisco, and informed consent, we studied seven healthy male volunteers, each on two separate days. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. The volunteers' demographic and morphometric characteristics included age, 28 ± 3 yr; height, 174 ± 5 cm; weight, 78 ± 9 kg; and body fat, 19 ± 2% (all mean ± SD).

Each participated on two study days, and at least 7 days were allowed between the study days in each volunteer. To avoid circadian fluctuations, studies were scheduled at the same time each day. The volunteers fasted for 8 h before each study day and rested supine on a standard operating room table. During the studies, they were minimally clothed, and ambient temperature was maintained near 21.5°C. Unless otherwise specified, all data were recorded at 5-min intervals.

Protocol

A catheter was inserted in a left forearm vein for fluid administration. Similarly, an arterial catheter was inserted into the left radial artery for hourly blood sampling. Lactated Ringer's solution warmed to 37°C was infused at ≈300 ml/h (Microwave Medical Systems Inc., Acton, MA). On each day, fever was induced by intravenous injection of 30 IU/g human recombinant interleukin-2 (IL-2; at elapsed time zero), followed 90 min later by 70 IU/g of the drug (Chiron, Inc., Berkeley, CA); this dose and timing was adapted from our previous fever study.[12]

Between the first and second elapsed hours, the volunteers were prewarmed[16,17] with a forced-air heater (Augustine Medical Inc., Eden Prairie, MN) at a high setting. Anesthesia was subsequently induced with intravenous propofol (≈5 mg/kg), and the volunteers' tracheas were intubated without administration of muscle relaxants. Volunteers were then randomly assigned to (1) no muscle relaxation or (2) paralysis with vecuronium bromide sufficient to maintain zero twitches in response to supermaximal electrical stimulation of the ulnar nerve at the wrist. In practice, this consisted of a loading dose of 0.1 mg/kg, followed by an infusion of 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$. Anesthesia was maintained for 6 h with isoflurane at an end-tidal concentration of 0.6% minimum alveolar concentration in 30% oxygen. A Foley catheter was inserted to prevent bladder distention.

On the unparalyzed study day, the volunteers breathed spontaneously, but ventilation was assisted when necessary to maintain end-tidal carbon dioxide pressure near 45 mmHg. On the vecuronium day, the mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide pressure near 45 mmHg. Paralysis was antagonized at the end of the study period with 0.035 mg/kg neostigmate and 0.005 mg/kg glycopyrrolate. Anesthesia was discontinued, and the volunteers' tracheas were extubated.

Anesthetic Data and Core Temperatures

End-tidal isoflurane and carbon dioxide concentrations were monitored using a Capnomac Ultima (Datex Medical Instruments, Tewksbury, MA). Blood pressures were determined oscillometrically at 5-min intervals at the left ankle. Arterial oxygen saturation and heart rates were measured using monitors incorporated into an Ohmeda Modulus CD anesthesia machine (Ohmeda Inc., Salt Lake City, UT).

Core temperature was recorded from the tympanic membrane using Mon-a-Therm thermocouples (Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO). The aural probes were 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 aural canal was occluded with

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-19980900-00014.pdf by guest on 20 April 2024

cotton, the probe taped securely in place, and a gauze bandage positioned over the external ear. Fingertip vasoconstriction was evaluated using forearm-minus-fingertip skin temperature gradients.[18] Values exceeding 0°C were considered evidence of arteriovenous shunt vasoconstriction.

Heat Balance and Tissue Heat Content

Energy expenditure, derived from oxygen consumption and carbon dioxide production, was measured using a metabolic monitor (Deltatrac, SensorMedics Corp., Yorba Linda, CA).[19,20] Measurements were averaged over 5-min intervals and recorded every 5 min. Area-weighted heat flux from 15 skin-surface sites was measured using thermal flux transducers (Concept Engineering, Old Saybrook, CT).[13] As in previous studies, measured cutaneous heat loss was augmented by 10% to account for insensible transcutaneous evaporative loss[21] and by 3% to compensate for the skin covered by the volunteers' shorts. We further augmented cutaneous loss by 5% of the metabolic rate (as determined from oxygen consumption) to account for respiratory loss.[22] We defined flux as positive when heat traversed skin to the environment.

Arm and leg (peripheral compartment) heat content was determined as previously described.[13] Briefly, the length of the thigh (groin to mid-patella) and lower leg (mid-patella to ankle) were measured in centimeters. Circumference was measured at the mid-upper thigh, mid-lower thigh, mid-upper calf, and mid-lower calf. At each circumference, right leg muscle temperatures were recorded using 8-, 18-, and 38-mm-long, 21-gauge needle thermocouples (Mallinckrodt Anesthesiology Products) inserted perpendicular to the skin surface. The lengths of the right arm (axilla to elbow) and forearm (elbow to wrist) were measured in centimeters. The circumference was measured at the mid-point of each segment. As in the right leg, 8-, 18-, and 38-mm-long needle thermocouples were inserted into each segment. Needle thermocouples were inserted shortly after anesthesia was induced. Skin-surface temperatures were recorded immediately adjacent to each set of needles.

All thermocouples were connected to calibrated Iso-Thermex thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments, Corp., Columbus, OH) or to Mon-a-Therm 6510 two-channel thermometers (Mallinckrodt Anesthesiology Products). Subcutaneous temperature was measured on the ball of the foot and palm of the hand using a Coretemp (Terumo Medical Corp., Tokyo, Japan) "deep tissue" thermometer.[23] This device estimates tissue temperature ≈1 cm below the skin surface.

The leg was divided into five segments: upper thigh, lower thigh, upper calf, lower calf, and foot. Each thigh and calf segment was further divided into an anterior and posterior section, with one third of the estimated mass considered to be posterior. Anterior segment tissue temperatures, as a function of the radial distance from the center of the leg segment, were calculated using skin-surface and muscle temperatures using fourth-order regressions. Temperature at the center of the thigh was set to core temperature. In contrast, temperature at the center of the lower leg segments was estimated from the regression equation with no similar assumption. The anterior limb heat content was estimated from these temperatures, as previously described.[24]

"Deep temperature," measured on the ball of the foot, was assumed to represent the entire foot. Foot heat content thus was calculated by multiplying foot temperature by the mass of the foot and the specific heat of muscle. Average temperatures of the thigh and lower leg (calf and foot) were calculated by weighting values from each of the nine segments in proportion to their estimated masses. Similarly, "deep temperature" measured on the palm was assumed to represent the entire hand and arm heat content was considered the weighted sum of the three arm segments. The right and left extremities were treated comparably throughout this study, so we assumed that average tissue temperatures on each side of the body were similar.

Changes in trunk and head heat content were modeled simply by multiplying the weight of the trunk and head by the change in core temperature and the average specific heat of human tissues. Trunk and head weight were estimated by subtracting the calculated weight of the extremities (from the radial integration) from the total weight of each volunteer.

Cytokines

Arterial blood was sampled for cytokine analysis at hourly intervals on the unparalyzed day. The samples were centrifuged at 300*g* for 20 min, and the plasma was separated and stored at −30°C until the assay. The following cytokines were evaluated: IL-2, IL-6, TNFα, and IL-10.

The biological activity of IL-2 was determined by an immunoenzomatic assay (IL-2 EASIA, Biosource Europe S.A., Fleurus, Belgium). Plasma IL-6 concentrations were measured by an enzyme-linked immunosorbent assay (Human Interleukin-6 ELISA Kit, Toray Industries, Tokyo,

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-199809000-00014.pdf by guest on 20 April 2024

Japan). The TNFα concentrations were determined by a human immunoassay (Quantikine HS, R&D Systems, Minneapolis, MN). Finally, plasma IL-10 concentrations were determined by a solid-phase enzyme-amplified immunoassay (IL-10 EASIA Kit, Medgenix Diagnostics S.A., Fleurus, Belgium). In each case, the assays were performed according to the manufacturers' directions, and appropriate calibration curves were constructed. All are highly specific and sensitive for the range of observed values.

Data Analysis

Administration of IL-2 was considered elapsed time zero. Metabolic rate, as determined by indirect calorimetry, was our primary measure of shivering. In addition, shivering was evaluated qualitatively by simple observation. Shivering was considered a distinct episode when muscular activity lasted at least 5 min and was followed by at least 5 quiescent min. As in previous investigations,[25] changes in whole-body heat content on each study day were calculated using two independent methods: (1) the time integral of metabolic heat production minus cutaneous heat loss, and (2) the sum of extremity and core tissue heat contents.

Febrile responses on each study day are presented as time-dependent changes. As suggested by Matthews,[26] our primary statistical analysis was based on curve descriptors. Specifically, we considered integrated core temperature, peak temperature, and the time to peak temperature. Values were integrated during the last 5 h of the anesthetic period with respect to average core temperatures during the first elapsed hour. Heat loss, heat production, and body heat content were similarly integrated during the last 5 h of anesthesia. (This period was chosen because peripheral tissue temperatures were unavailable during the first hour of anesthesia while needle thermocouples were being inserted.) Systemic heat balance was calculated by subtracting integrated heat loss from integrated heat production.

End-tidal carbon dioxide pressure, ambient temperature, humidity, mean arterial blood pressure, heart rate, and administered fluid volume were first averaged for the anesthetic period in each volunteer on each study day. Subsequently, these values were averaged among the volunteers undergoing each treatment. Differences between the paralyzed and unparalyzed study days were evaluated using two-tailed, paired t tests. Data are presented as mean ± SD; $P < 0.05$ was considered significant.

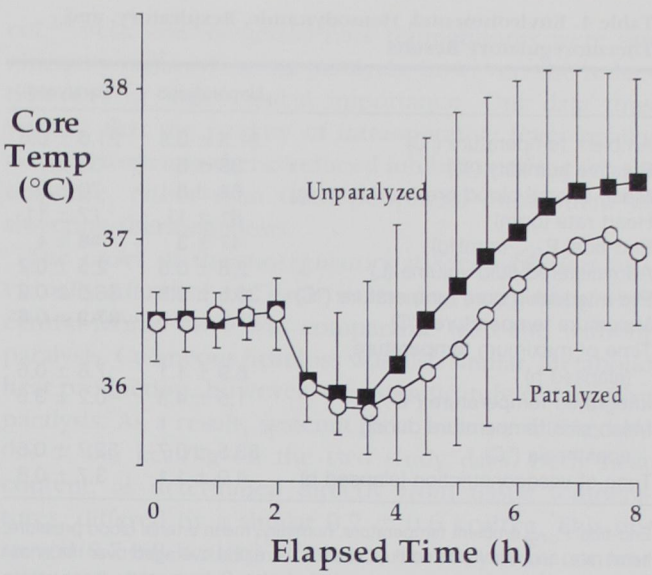

Fig. 1. Change in core temperature after administration of 30 IU/g interleukin-2 (IL-2), followed 90 min later by an additional dose of 70 IU/g. The first dose of IL-2 defined elapsed time zero; anesthesia started after 2 elapsed h and continued for 6 h. Data are presented as mean ± SD. Peak and integrated core temperatures differed significantly during the anesthesia period; however, the difference was not clinically important.

Results

The estimated mass of legs was 30 ± 4 kg, whereas the mass of the arms was 8 ± 1 kg. Consequently, peripheral tissue represented 49 ± 5% of our volunteers' total mass. Ambient temperatures, humidity, mean arterial blood pressures, end-tidal carbon dioxide pressure, and administered fluid volumes were comparable on the two treatment days. Heart rates were not significantly higher on the unparalyzed day (81 ± 11 *vs.* 78 ± 11 beats/min).

The onset of vasoconstriction was similar in each group at 4 ± 1.1 elapsed h in the unparalyzed day and 3.7 ± 0.6 h when the volunteers were paralyzed. Once initiated, vasoconstriction persisted throughout the rest of the protocol on both treatment days. Shivering started a median of 35 min (−16 min for the 25th and 40 min for the 75th percentile) after the onset of vasoconstriction on the unparalyzed day and lasted 61 ± 28 min. There were 4 ± 1 shivering episodes per volunteer during the anesthesia period. No shivering was observed on the paralyzed day.

Initial (before interleukin) core temperatures were comparable on the two study days, averaging 36.5°C on each. Induction of general anesthesia comparably decreased core temperature ≈0.8°C on each study day. Peak core temperatures differed significantly on the two

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-199809000-00014.pdf by guest on 20 April 2024

Table 1. Environmental, Hemodynamic, Respiratory, and Thermoregulatory Results

	Unparalyzed	Paralyzed
Ambient temperature (°C)	21.3 ± 0.5	21.6 ± 0.5
Relative humidity (%)	38 ± 8	39 ± 7
Mean arterial blood pressure (mmHg)	64 ± 8	70 ± 9
Heart rate (bpm)	81 ± 11	77 ± 11
End-tidal P_{CO_2} (mmHg)	47 ± 3	48 ± 4
Administered fluid volume (L)	2.8 ± 0.5	2.5 ± 0.2
Pre-interleukin core temperature (°C)	36.5 ± 0.3	36.5 ± 0.2
Maximum temperature (°C)	37.6 ± 0.9	37.2 ± 0.6*
Time of maximum temperature (elapsed h)	6.9 ± 1.1	7.6 ± 0.6
Integrated temperature (°C · h)	1.5 ± 4.3	−0.2 ± 3.5*
Mean skin temperature during anesthesia (°C)	33.5 ± 0.7	32.7 ± 0.5*
Time of vasoconstriction (elapsed h)	4.0 ± 1.1	3.7 ± 0.6

End-tidal P_{CO_2}, ambient temperature, humidity, mean arterial blood pressure, heart rate, and administered fluid volume were first averaged over the anesthetic period in each volunteer on each study day. Subsequently, these values were averaged among the volunteers undergoing each treatment. Data are mean ± SD.

* Statistically significant differences between the two study days.

study days, reaching 37.6 ± 0.9°C after 6.9 ± 1.2 h on the unparalyzed day and 37.2 ± 0.6°C after 7.6 ± 0.5 h on the paralyzed day (fig. 1). Integrated core temperature (from the third to the eighth elapsed hours) was 1.5 ± 4.3°C/h on the unparalyzed day *versus* −0.2 ± 3.5°C/h on the paralyzed day; these values differed significantly by 1.7 ± 1.1°C/h (table 1).

Heat losses (integrated over 3–8 elapsed h) were similar on each study day. In contrast, integrated heat production was 0.6 ± 0.3 kcal · kg^{-1} · h^{-1} greater when the volunteers were unparalyzed. Systemic heat balance, defined by the difference between heat production and loss, thus increased 0.5 ± 0.8 kcal/kg on the unparalyzed day but decreased significantly by 0.3 ± 0.6 kcal/kg when the volunteers were paralyzed (fig. 2).

Core heat content increased 1.2 ± 0.7 kcal/kg over 3–8 elapsed h on the unparalyzed day, and 0.9 ± 0.4 kcal/kg when the volunteers were paralyzed. Peripheral tissue heat content increased 0.1 ± 1.1 kcal/kg on the unparalyzed day, but it decreased 1.1 ± 0.7 kcal/kg when the volunteers were paralyzed (fig. 3). Consequently, body heat content (as defined by tissue temperatures) increased 1.3 ± 1.3 kcal/kg on the unparalyzed day but decreased 0.2 ± 0.8 kcal/kg when the volunteers were paralyzed. Changes in body heat content estimated from tissue temperatures did not differ significantly from those determined from systemic heat production and loss.

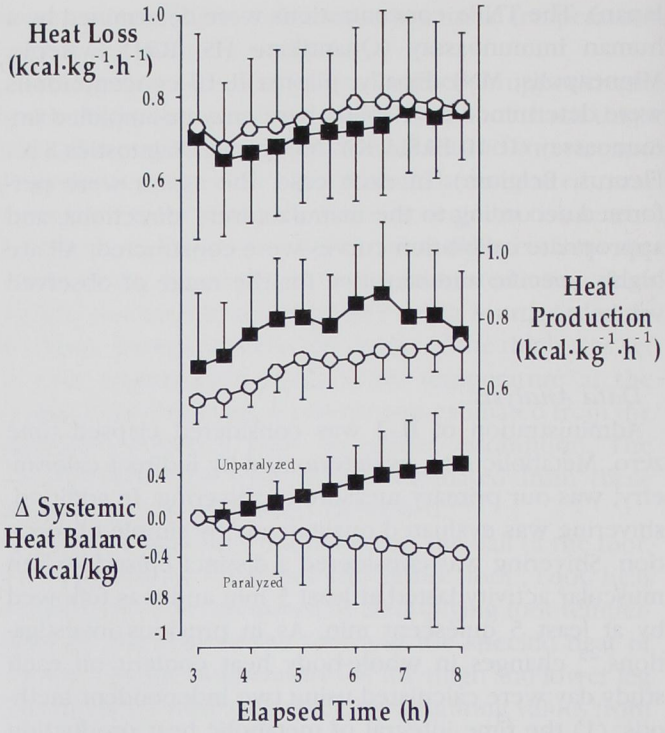

Fig. 2. Heat loss was similar on the unparalyzed and on the paralyzed study day. In contrast, metabolic heat production was consistently higher on the unparalyzed study day. Systemic heat balance increased on the unparalyzed day during the anesthesia period, whereas it decreased on the paralyzed day. The first dose of interleukin-2 defined elapsed time zero; anesthesia started after 2 elapsed h and continued for 6 h. Results for the last 5 h of anesthesia are shown because peripheral tissue temperatures were unavailable during the first hour of anesthesia while needle thermocouples were being inserted. Data are presented as mean ± SD.

The core-to-peripheral tissue temperature gradients at 3 elapsed h were comparable on the unparalyzed and paralyzed days: 1.2 ± 0.6°C and 1.3 ± 0.4°C, respectively. Core temperatures increased significantly during anesthesia, but there were no clinically important differences on the two study days after 8 elapsed h. Peripheral tissue temperature remained unchanged on the unparalyzed day, but it decreased 1.2 ± 0.6°C with paralysis. Consequently, the core-to-peripheral tissue temperature gradient was significantly less on the paralyzed (2.6 ± 1.0°C) than on the unparalyzed (3.5 ± 1.1°C) study day (table 2).

Plasma concentrations of IL-2, which were essentially undetectable at elapsed time zero, increased to 19 ± 2 IU/ml 1 h after the first dose and peaked at 224 ± 68 IU/ml after the second hour. Plasma concentrations of TNF increased 13 times from pretreatment levels to peak levels 3.5 ± 1.4 h after the first dose of IL-2. The IL-6

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-19980900-00014.pdf by guest on 20 April 2024

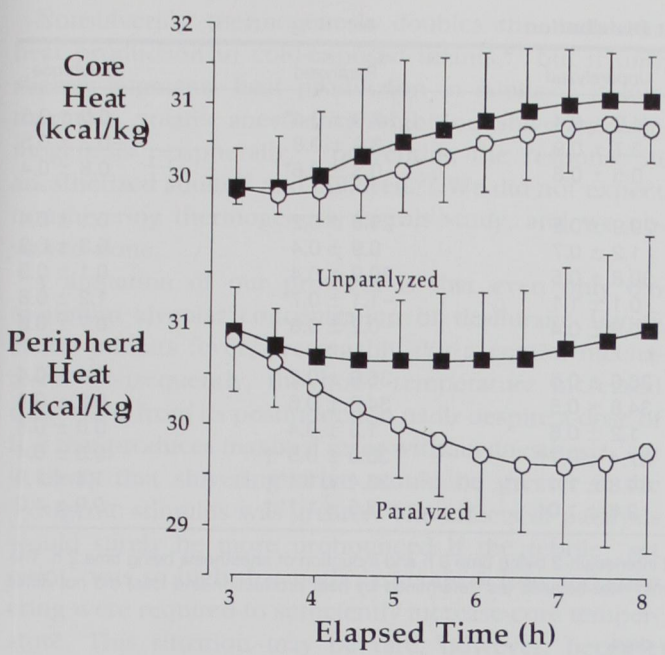

Fig. 3. Core heat content increased significantly during anesthesia on the unparalyzed and on the paralyzed study day. Peripheral heat content changed little on the unparalyzed day but decreased markedly when the volunteers were paralyzed. Consequently, the core-to-peripheral tissue temperature gradient at the end of anesthesia was significantly higher with paralysis. The first dose of interleukin-2 defined elapsed time zero; anesthesia started after 2 elapsed h and continued for 6 h. Results for the last 5 h of anesthesia are shown because peripheral tissue temperatures were unavailable during the first hour of anesthesia while needle thermocouples were being inserted. Data are presented as mean ± SD.

concentrations were 9 ± 13 pg/ml before treatment and increased nine times to peak levels at 5.7 ± 1.4 elapsed h. Pretreatment concentrations of IL-10 were undetectable. The concentrations subsequently increased in all volunteers, but the pattern varied. IL-10 differed from the other cytokines in not returning toward baseline values by the end of the study (fig. 4).

The volunteers remained hemodynamically stable throughout the protocol. Some of the volunteers reported postanesthetic headache or sore muscles. When necessary, residual fever, headache, or sore muscles were treated with 500 mg oral aspirin. None of the volunteers was nauseated or vomited. Typically the volunteers recovered quickly and were fit for discharge 3 or 4 h after anesthesia.

Discussion

The fever pattern in our unparalyzed volunteers was comparable to that observed in a previous similar protocol.[12] Peak and integrated core temperatures were significantly reduced during paralysis; however, the reduction was of little clinical importance. Our data thus suggest that the paucity of intraoperative fever results directly from anesthetic-induced inhibition of the febrile response, rather than from peripheral impairment of shivering thermogenesis.

The onset of thermoregulatory vasoconstriction was virtually identical on each study day, suggesting that central febrile drive was comparable with and without paralysis. Cutaneous heat loss was also similar. Metabolic heat production, however, was significantly reduced by paralysis. As a result, systemic heat balance differed by 0.8 ± 0.4 kcal/kg on the two study days. Body heat content, as determined directly from tissue temperatures, differed by a similar 0.7 ± 0.6 kcal/kg. This observed 0.7-0.8 kcal/kg difference in body heat content corresponds to a difference in mean body temperature of 0.8 to 0.9°C, which might well be clinically important. Based on heat balance alone, one might therefore conclude that shivering was effective. So why, then, was the difference in core temperature only half that much? The answer is that body heat distribution also differed.

Peripheral tissue temperatures, which were initially comparable, decreased by about 1°C during anesthesia with paralysis; core temperature simultaneously increased by approximately 1°C. Consequently, the core-to-peripheral temperature gradient increased more than 2°C. The increase in core temperature was similar when the volunteers were unparalyzed, but peripheral temperatures remained unchanged because shivering thermogenesis produced substantial amounts of heat in large extremity muscles. The core-to-peripheral temperature gradient thus increased only half as much when the volunteers were unparalyzed. Thermoregulatory vasoconstriction nonetheless contributed significantly to fever on both the paralyzed and unparalyzed days, significantly increasing the core-to-peripheral tissue temperature gradient in each case.

Vasoconstriction was the only mechanism that contributed to fever during paralysis. Fever in this case resulted from an effective constraint of metabolic heat to the core thermal compartment. (This is the same mechanism that causes the core-temperature plateau in patients having surgery who become sufficiently hypothermic.[14]) In contrast, shivering thermogenesis was sufficient to prevent the peripheral cooling that normally accompanies vasoconstriction. Vasoconstriction was thus less effective during shivering (in that it maintained a lower core-to-peripheral tissue temperature gradient), but there are

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-19980900-00014.pdf by guest on 20 April 2024

Table 2. Integrated Core Temperatures, Heat Balance, and Body Heat Distribution

	Unparalyzed	Paralyzed	Difference
Integrated heat production (kcal · kg^{-1} · h)	4.2 ± 0.4	3.6 ± 0.4*	0.6 ± 0.3
Integrated heat loss (kcal · kg^{-1} · h)	3.7 ± 0.9	3.9 ± 0.8	−0.2 ± 0.5
Δ Systemic heat balance from 3–8 h (kcal/kg)	0.5 ± 0.8	−0.3 ± 0.6*	0.8 ± 0.4
Core heat content at 3 h (kcal/kg)	29.9 ± 0.5	29.8 ± 0.2	0.1 ± 0.4
Δ Core heat content from 3–8 h (kcal/kg)	1.2 ± 0.7	0.9 ± 0.4	0.3 ± 0.3
Peripheral heat content at 3 h (kcal/kg)	30.8 ± 0.5	30.9 ± 0.4	0.1 ± 0.3
Δ Peripheral heat content from 3–8 h (kcal/kg)	0.1 ± 1.1	−1.1 ± 0.7*	1.2 ± 0.8
Δ Body heat content from 3–8 h (kcal/kg)	0.5 ± 0.4	−0.2 ± 0.8*	0.7 ± 0.6
Core temperature at 3 h (°C)	36.0 ± 0.5	35.9 ± 0.2	0.1 ± 0.4
Peripheral tissue temperature at 3 h (°C)	34.8 ± 0.5	34.6 ± 0.6	0.2 ± 0.4
Core-to-peripheral tissue temperature difference at 3 h (°C)	1.2 ± 0.6	1.3 ± 0.4	0.0 ± 0.6
Core temperature at 8 h (°C)	37.4 ± 0.7†	36.9 ± 0.5*†	0.5 ± 0.4
Peripheral tissue temperature at 8 h (°C)	34.8 ± 1.1	33.4 ± 1.1*†	1.4 ± 1.0
Core-to-peripheral tissue temperature difference at 8 h (°C)	2.6 ± 1.0†	3.5 ± 1.1*†	−0.9 ± 1.0

Data are means ± SD. All times expressed in elapsed hours, with the first dose of interleukin-2 being time 0 h and induction of anesthesia being time 2 h. The changes in body heat content (as determined by tissue temperatures) and systemic heat balance (as determined by heat production and loss) did not differ significantly.

* Statistically significant differences between the unparalyzed and paralyzed study days.

† Significant differences between 3 and 8 elapsed hours.

two possible explanations: (1) There was less central drive for vasoconstriction because low-intensity constriction was sufficient to reach the febrile target temperature; (2) blood supplying the metabolic needs of shivering peripheral muscles defeated effective vasoconstriction. It is unlikely, however, that shivering would be used in preference to vasoconstriction because the threshold for shivering is ≈1°C less than that for constriction.[27] It therefore seems most likely that the metabolic needs of shivering extremity muscles reduced the efficacy of vasoconstriction. Efficacy in this context, as in previous studies,[13,25] was mediated by changes in the core-to-peripheral temperature gradient rather than cutaneous heat loss. Increased peripheral blood flow is one reason why shivering is inefficient compared with nonshivering thermogenesis. The other is that heat generated in the extremities cannot travel up the peripheral-to-core thermal gradient to where it is most needed.

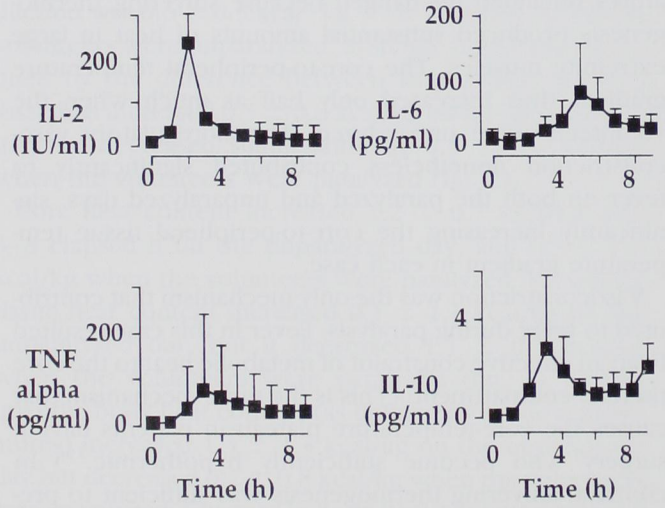

Fig. 4. Interleukin 2 (IL-2), IL-6, tumor necrosis factor alpha, and IL-10 plasma concentrations are shown at hourly intervals. The first blood sample was taken just before administration of the first IL-2 dose (elapsed time zero). Data are presented as mean ± SD.

Fever in our volunteers was provoked by divided intravenous doses of IL-2. Not surprisingly, plasma IL-2 concentrations increased from essentially undetectable levels to >200 IU/ml 30 min after the second dose. IL-2 is an indirect pyrogen; it thus causes fever by triggering release of primary pyrogens.[3–7] Consistent with this mechanism, TNFα and IL-6 both increased approximately 10 times and peaked about 3 h later during the rising phase of the fever curve. IL-10 differs from other cytokines in being anti-inflammatory, and it is thought to moderate the febrile response to other pyrogens.[28] Consistent with this theory, IL-10 plasma concentrations started to increase shortly after the second dose of IL-2 but then remained elevated for the duration of the study. We measured cytokine concentrations only on the unparalyzed day because we had no reason to expect that a peripheral neuromuscular block would influence circulating IL-2, IL-6, TNFα, or IL-10 levels.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-19980900-00014.pdf by guest on 20 April 2024

Nonshivering thermogenesis doubles the metabolic heat production in cold-exposed infants,[29] but it only slightly augments heat production in adults.[30–32] Furthermore, volatile anesthetics inhibit nonshivering thermogenesis peripherally,[33] preventing the response in anesthetized adults[34] and children.[35] We did not expect nonshivering thermogenesis in this study, and we observed none.

A limitation of our protocol is that even only 0.6 minimum alveolar concentration of desflurane significantly inhibits fever, presumably *via* a central mechanism. Consequently, the body temperature increased only ≈1°C from its postinduction nadir despite a dose of IL-2 that produces maximal fever without anesthesia.[12] It is likely that shivering drive would be greater if the pyrogenic stimulus was greater. The effects of paralysis would surely be more pronounced if the febrile "set point" was so high that both vasoconstriction and shivering were required to sufficiently increase core temperature. This situation may be rare, however, because clinical concentrations of volatile anesthetics (*i.e.*, 1 minimum alveolar concentration) essentially obliterate fever.[12] Even if a particularly potent pyrogenic stimulus could overcome anesthetic-induced inhibition of fever, the effects of intraoperative paralysis may be less than expected because volatile anesthetics also reduce the maximum intensity of shivering.[36]

In conclusion, paralysis prevented shivering from increasing metabolic rate. Consequently, body heat content decreased during paralysis, whereas otherwise it increased. Thermoregulatory vasoconstriction nonetheless maintained similar peak and integrated core temperatures on each study day. Administration of muscle relaxants thus is not the primary explanation for the relative paucity of intraoperative fever.

The Coretemp "deep tissue" thermometer was loaned by Terumo Medical Corp., Tokyo, Japan. Other equipment was donated by the following: thermocouples, Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO; Capnomac Ultima gas monitor, Datex, Inc., Finland; and intravenous fluid warmer, Microwave Medical Systems Inc., Acton, MA.

References

1. Kanosue K, Yanase-Fujiwara M, Hosono T: Hypothalamic network for thermoregulatory vasomotor control. Am J Physiol 1994; 267:R283–8

2. Kanosue K, Zhang Y-H, Yanase-Fujiwara M, Hosono T: Hypothalamic network for thermoregulatory shivering. Am J Physiol 1994; 267:R275–82

3. Dinarello CA, Cannon JG, Mier JW, Bernheim HA, LoPreste G, Lynn DL, Love RN, Webb AC, Auron PE, Reuben RC, Rich A, Wolff SM, Putney SD: Multiple biological activities of human recombinant interleukin 1. J Clin Invest 1986; 77:1734–9

4. Dinarello CA, Cannon JG, Wolff SM, Bernheim HA, Beutler B, Cerami A, Figari IS, Palladino JMA, O'Connor JV: Tumor necrosis factor (cachectin) is an endogenous pyrogen and induces production of interleukin 1. J Exp Med 1986; 163:1433–50

5. Dinarello CA, Cannon JG, Mancilla J, Bishai I, Lees J, Coceani F: Interleukin-6 as an endogenous pyrogen: Induction of prostaglandin E2 in brain but not in peripheral blood mononuclear cells. Brain Res 1991; 562:199–206

6. Dinarello CA, Bernheim HA, Duff GW, Le HV, Nagabhushan TL, Hamilton NC, Coceani F: Mechanisms of fever induced by recombinant human interferon. J Clin Invest 1984; 74:906–13

7. Davatelis G, Wolpe SD, Sherry B, Dayer JM, Chicheportiche R, Cerami A: Macrophage inflammatory protein-1: A prostaglandin-independent endogenous pyrogen. Science 1989; 243:1066–8

8. Romanovsky AA, Simons CT, Szekely M, Kulchitsky VA: The vagus nerve in the thermoregulatory response to systemic inflammation. Am J Physiol 1997; 273:R407–13

9. Goldbach JM, Roth J, Zeisberger E: Fever suppression by subdiaphragmatic vagotomy in guinea pigs depends on the route of pyrogen administration. Am J Physiol 1997; 272:R675–81

10. Sehic E, Blatteis CM: Blockade of lipopolysaccharide-induced fever by subdiaphragmatic vagotomy in guinea-pigs. Brain Res 1996; 726:160–6

11. Boulant JA: Thermoregulation, Fever: Basic Mechanisms and Management, 2nd ed. Edited by PA Mackowiak. New York, Lippincott-Raven, 1997, pp 35–58

12. Negishi C, Lenhardt R, Sessler DI, De Witte J, Ikeda T, Kurz A, Lobo E: Desflurane reduces the febrile response to interleukin-2 administration. ANESTHESIOLOGY 1998; 88:1162–9

13. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C: Heat flow and distribution during induction of general anesthesia. ANESTHESIOLOGY 1995; 82:662–73

14. Kurz A, Sessler DI, Christensen R, Dechert M: Heat balance and distribution during the core-temperature plateau in anesthetized humans. ANESTHESIOLOGY 1995; 83:491–9

15. Plattner O, Ikeda T, Sessler DI, Christensen R, Turakhia M: Postanesthetic vasoconstriction slows postanesthetic peripheral-to-core transfer of cutaneous heat, thereby isolating the core thermal compartment. Anesth Analg 1997; 85:899–906

16. Hynson JM, Sessler DI, Moayeri A, McGuire J, Schroeder M: The effects of pre-induction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia. ANESTHESIOLOGY 1993; 79: 219–28

17. Just B, Trévien V, Delva E, Lienhart A: Prevention of intraoperative hypothermia by preoperative skin-surface warming. ANESTHESIOLOGY 1993; 79:214–8

18. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. ANESTHESIOLOGY 1990; 73:541–5

19. Merilainen PT: Metabolic monitor. Int J Clin Monit Comput 1987; 4:167–77

20. Tissot S, Delafosse B, Bertrand O, Bouffard Y, Viale JP, Annat G: Clinical validation of the Deltatrac monitoring system in mechanically ventilated patients. Int Care Med 1995; 21:149–53

21. Hammarlund K, Sedin G: Transepidermal water loss in newborn infants III. Relation to gestational age. Acta Paediatr Scand 1979; 68:795–801

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-199809000-00014.pdf by guest on 20 April 2024

22. Bickler P, Sessler DI: Efficiency of airway heat and moisture exchangers in anesthetized humans. Anesth Analg 1990; 71:415–8

23. Togawa T, Nemoto T, Yamazaki T, Kobayashi T: A modified internal temperature measurement device. Med Biol Eng 1976; 14: 361–4

24. Belani K, Sessler DI, Sessler AM, Schroeder M, McGuire J, Washington D, Moayeri A: Leg heat content continues to decrease during the core temperature plateau in humans. ANESTHESIOLOGY 1993; 78:856–63

25. Matsukawa T, Sessler DI, Christensen R, Ozaki M, Schroeder M: Heat flow and distribution during epidural anesthesia. ANESTHESIOLOGY 1995; 83:961–7

26. Matthews JNS, Altman DG, Campbell MJ, Royston P: Analysis of serial measurements in medical research. BMJ 1990; 300:230–5

27. Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. ANESTHESIOLOGY 1994; 80:780–8

28. Nava F, Calapai G, Facciola G, Cuzzocrea S, Marciano MC, De Sarro A, Caputi AP: Effects of interleukin-10 on water intake, locomotory activity, and rectal temperature in rat treated with endotoxin. Int J Immunopharmacol 1997; 19:31–8

29. Dawkins MJR, Scopes JW: Non-shivering thermogenesis and brown adipose tissue in the human new-born infant. Nature 1965; 206:201–2

30. Jessen K: An assessment of human regulatory nonshivering thermogenesis. Acta Anaesthesiol Scand 1980; 24:138–43

31. Jessen K, Rabøl A, Winkler K: Total body and splanchnic thermogenesis in curarized man during a short exposure to cold. Acta Anaesthesiol Scand 1980; 24:339–44

32. Brück K, Baum E, Schwennicke HP: Cold-adaptive modifications in man induced by repeated short-term cold-exposures and during a 10-day and -night cold-exposure. Pflügers Arch 1976; 363:125–33

33. Dicker A, Ohlson KB, Johnson L, Cannon B, Lindahl SG, Nedergaard J: Halothane selectively inhibits nonshivering thermogenesis. ANESTHESIOLOGY 1995; 82:491–501

34. Hynson JM, Sessler DI, Moayeri A, McGuire J: Absence of nonshivering thermogenesis in anesthetized humans. ANESTHESIOLOGY 1993; 79:695–703

35. Plattner O, Semsroth M, Sessler DI, Papousek A, Klasen C, Wagner O: Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. ANESTHESIOLOGY 1997; 86:772–7

36. Ikeda T, Kim J-S, Sessler DI, Negishi C, Turakhia M, Jeffrey R: Isoflurane alters shivering patterns and reduces maximum shivering intensity. ANESTHESIOLOGY 1998; 88:866–73

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/3/648/394724/0000542-19980900-00014.pdf by guest on 20 April 2024