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Desflurane Reduces the Febrile Response to Administration of Interleukin-2

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Background: **Intraoperative fever is relatively rare considering how often pyrogenic causes are likely to be present and how common fever is postoperatively. This low incidence suggests that general anesthesia *per se* inhibits the normal response to pyrogenic stimulation. The authors therefore tested the hypothesis that desflurane-induced anesthesia produces a dose-dependent inhibition of the febrile response.**

Methods: **Eight volunteers were studied, each on 3 study days. Each was given an intravenous injection of 50,000 IU/kg of interleukin-2 (elapsed time, 0 h), followed 2 h later by 100,000 IU/kg. One hour after the second dose, the volunteers were assigned randomly to three doses of desflurane to induce anesthesia: (1) 0.0 minimum alveolar concentration (MAC; control), (2) 0.6 MAC, and (3) 1.0 MAC. Anesthesia continued for 5 h. Core temperatures were recorded from the tympanic membrane. Thermoregulatory vasoconstriction was evaluated using forearm-minus-fingertip skin temperature gradients; shivering was evaluated with electromyography. Integrated and peak temperatures during anesthesia were compared with repeated-measures analysis of variance and Scheffé's F tests.**

Results: **Values are presented as mean ± SD. Desflurane reduced the integrated (area under the curve) febrile response to pyrogen, from 7.7 ± 2.0°C · h on the control day to 2.1 ± 2.3°C · h during 0.6 MAC and to −1.4 ± 3.1°C · h during 1.0 MAC desflurane-induced anesthesia. Peak core temperature (elapsed time, 5–8 h) decreased in a dose-dependent fashion: 38.6 ± 0.5°C on the control day, 37.7 ± 0.7°C during 0.6 MAC and 37.2 ± 1.0°C during 1.0 MAC desflurane anesthesia. Rising core temperature was always associated with fingertip vasoconstriction and often with shivering.**

Conclusions: **Desflurane-induced anesthesia produced a dose-dependent decrease in integrated and peak core temperatures after administration of pyrogen, with 1.0 MAC essentially obliterating fever. Anesthetic-induced inhibition of the pyrogenic response is therefore one reason that fever is an inconsistent clinical response to inflammation during surgery. (Key words: Anesthesia; hyperthermia; pyrogen; temperature; thermoregulation.)**

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 (IL)-1, IL-6, tumor necrosis factor, and interferon-α.[3–6] It is likely, however, that other factors, including macrophage inflammatory protein, also contribute.[7] The mechanisms by which pyrogens activate hypothalamic control centers remain controversial, but there is considerable evidence that vagal afferents are involved.[8–12] Fever synchronously augments thermoregulatory response thresholds (triggering core temperatures[13]), which can be considered an increase in the "set point." Core temperature elevation then results from activation of cold defenses, including vasoconstriction and shivering.[12]

In many cases, fever is protective or provides a useful warning to clinicians[14–16]; in others, however, the asso-

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ciated tachycardia, shivering, and thermal discomfort themselves become problematic. The pathophysiology of fever and the efficacy of various treatments in patients remain poorly understood because no human model has been available. (Although fever is common, it is a sporadic response, with an unpredictable magnitude.) Our first goal, therefore, was to develop a human model of fever, using IL-2, a cytokine approved by the Food and Drug Administration for the treatment of renal cell cancer[17–19] and human immunodeficiency virus infections.[20,21] Interleukin-2 is an indirect pyrogen that produces fever by stimulating release of IL-1, tumor necrosis factor, and other primary pyrogens.[22–24]

Causes of perioperative fever include infection, noninfectious inflammation, allergic reactions, and blood in the fourth cerebral ventricle. Intraoperative fever is relatively rare, however, considering how often pyrogenic stimuli are likely to be present during surgery and how common fever is postoperatively. This low incidence suggests that general anesthesia *per se* inhibits the normal febrile response to pyrogenic stimulation. Accordingly, we tested the hypothesis that desflurane-induced anesthesia produces a dose-dependent inhibition of the febrile response to pyrogenic stimulation.

Methods

With approval from the Committee on Human Research at the University of California, San Francisco, and written informed consent, we studied two sets of healthy male volunteers. None was obese; was taking medication; or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. 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 22°C.

Dose Range Protocol

To determine the appropriate dose of IL-2, we evaluated 21 unanesthetized volunteers on 35 occasions. Intervals between repeated study days in the same volunteer ranged from 7 to 53 days and averaged 17 days. Fever was induced by intravenous injection of 30,000–150,000 IU/kg human recombinant IL-2 (Chiron, Inc., Berkeley, CA).

Because this was a dose range study, rather than a formal protocol, the tested doses were not given in any specific order but were instead based on our qualitative assessment of responses in the previous volunteers. On 7 study days, pyrogen was administered as a single bolus dose. Interleukin-2 stimulation of T cells, however, causes additional expression of specific IL-2 receptors (with a turnover rate of at least 6 h). The long half-life of the receptors leads to accumulation of the receptors on the surface of activated T cells, where additional IL-2 may be easily bound.[25,26] To facilitate the febrile response, we therefore often gave an initial small dose to activate immunologic responses, followed by one (n = 22) or two (n = 5) doses administered over a 1- to 2-h interval.

In the initial studies, little intravenous fluid was given; in subsequent volunteers, lactated Ringer's solution at ambient temperature was infused at ≈300 ml/h. Volunteers were covered with two cotton blankets throughout the study.

Desflurane Protocol

To determine the effect of desflurane-induced anesthesia on the pyrogenic responses, we evaluated eight healthy male volunteers, each on 3 study days. All studies were conducted in spring 1997. To avoid circadian fluctuations, studies were scheduled so that thermoregulatory responses were triggered at similar times on each of the 3 days. A catheter was inserted in a left forearm vein for fluid administration. Lactated Ringer's solution at ambient temperature was infused at ≈300 ml/h. On each day, the volunteers were given an intravenous injection of 50,000 IU/kg of human recombinant IL-2, followed 2 h later by 100,000 IU/kg of the drug. (We are not aware that IL-2 and general anesthesia have been combined previously. Consequently, we performed several preliminary studies, first with low and then progressively higher doses of IL-2, to be sure that the volunteers would not experience any unexpected synergistic toxicity at our chosen dose.)

Each volunteer was given three end-tidal concentrations of desflurane in a randomly assigned order: (1) control (0.0 minimum alveolar concentration [MAC]), (2) 0.6 MAC, and (3) 1.0 MAC (7%). The treatment order was randomly determined, and at least 5 days were allowed between treatments. Anesthesia started 1 h after the second dose of IL-2 and continued for 5 h. During the hour before induction of anesthesia, the volunteers were warmed with forced air (on low setting) to prevent excessive redistribution hypothermia.[27] Otherwise, the volunteers were covered only by a single blanket throughout the entire study.

On the 0.6 MAC and 1.0 MAC days, anesthesia was

induced without any premedication by infusion of propofol (≈5 mg/kg) and incremental concentrations of desflurane. The trachea was intubated without administration of muscle relaxants. The volunteers breathed spontaneously, but ventilation was assisted when necessary to maintain end-tidal partial pressure of carbon dioxide at ≈45 mmHg. On anesthesia days, a Foley catheter was inserted to prevent bladder distention.

Measurements

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 cotton, the probe securely taped in place, and a gauze bandage positioned over the external ear. Temperatures were recorded at 5-min intervals from thermocouples connected to a calibrated Iso-Thermex® thermometer (Columbus Instruments Corp., Columbus, OH) with an accuracy of 0.1°C and a precision of 0.01°C.

Shivering was evaluated electromyographically during the desflurane protocol. After mild skin abrasion and degreasing, silver/silver chloride monitoring electrodes were positioned to record the electrical activity of the right pectoralis, trapezius, rectus abdominis, and the quadriceps femoris. The active electrodes were positioned 4 cm apart and oriented in the direction of the muscle fibers.[28] After appropriate amplification (model P511; Grass Instruments, Quincy, MA), the signals were recorded on a thermoelectric printer (Dash-4; Astro-Med, West Warwick, RI) with a linear resolution to 1,000 Hz. Signals were also digitized for computer analysis at 1,000 Hz (models NB-MIO-16H and NB-DMA-2800; LabVIEW 3.11, National Instruments, Austin, TX), and root-mean square values of 1-min acquisition intervals were computed.

Heart rate was measured continuously using pulse oximetry, and blood pressure was determined oscillometrically at 5-min intervals at the left ankle. End-tidal carbon dioxide concentrations during anesthesia were measured with an Ultima® monitor (Datex, Helsinki, Finland). Vasoconstriction was evaluated using the perfusion index, a pulse oximeter–based system. Potential side effects, including chills, nausea, and headache, also were recorded.

Data Analysis

The first dose of IL-2 was considered elapsed time 0 h in both protocols. In the dose range study, average onset times for vasoconstriction and fever exceeding 38°C were computed. The maximum change in core temperature and duration of fever at various doses of IL-2 were similarly determined.

Febrile responses at each concentration of desflurane were presented as time-dependent changes. As suggested by Matthews *et al.*,[29] 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 over the anesthetic period, with respect to the mean temperature during the first elapsed hour. That is, we calculated the area under the temperature curve. This quantified the extent to which core temperature exceeded initial values (in °C · h) and is a standard way of expressing fever intensity. Ambient temperature and humidity, hemodynamic responses, end-tidal partial pressure of carbon dioxide and the volume of administered fluid during the anesthetic period on each study day were first averaged within each volunteer; the resulting values were then averaged among volunteers.

Most results for the 3 study days were compared using repeated-measures analysis of variance and Scheffé's F tests. One-way analysis of variance and Scheffé's F tests were used for peak temperature and time to the peak temperature because values were not available for every volunteer for each condition. End-tidal partial pressure of carbon dioxide values at each anesthetic concentration were compared using two-tailed, paired *t* tests. Second-order polynomial regression was used to evaluate the relation between core temperature change and the percent increase in heart rate on the control days of the desflurane protocol. All values between 0 and 10 elapsed h were included in this analysis, after being averaged into 30-min blocks. Results are presented as the mean ± SD; a probability value <0.05 was considered statistically significant.

Results

Morphometric and demographic characteristics of the volunteers participating in each protocol were similar (table 1).

Dose Range Protocol

Fever was monophasic. Onset of the peak temperature was 6 ± 1 h and did not correlate with the dose

Table 1. Morphometric and Demographic Characteristics of the Volunteers

	Dose Range	Desflurane
No.	21	8
Age (yr)	29 ± 4	30 ± 4
Weight (kg)	73 ± 8	76 ± 9
Height (cm)	172 ± 5	172 ± 5

Data are mean ± SD. There were no statistically significant differences among the volunteers participating in each protocol. The control days for all volunteers in the desflurane protocol were included in the dose ranging analysis.

of IL-2. Fever magnitude and duration increased to a total dose of 100,000 IU/kg but subsequently failed to increase further. At that dose, fever magnitude was 1.8 ± 0.5°C, and the duration was 3.1 ± 2.0 h (fig. 1).

Fingertip vasoconstriction was observed in all but one volunteer; time of onset was 3 ± 1 h, and constriction generally continued throughout the study period. Tachycardia (heart rate >100 beats/min) was observed in 70% of volunteers, 80% reported chills, and 34% shivered. Some volunteers developed nausea (14%) and vomiting (9%); however, no severe complications, such as supine hypotension or sepsis syndrome, were observed. Mild postural hypotension was observed in the initial studies but was no longer problematic in volunteers given larger amounts of intravenous fluid. Some volunteers also experienced somnolence and mild myalgias. There was no evidence of tolerance in the volunteers who participated on more than one study day, nor did there appear to be any progressive toxicity.

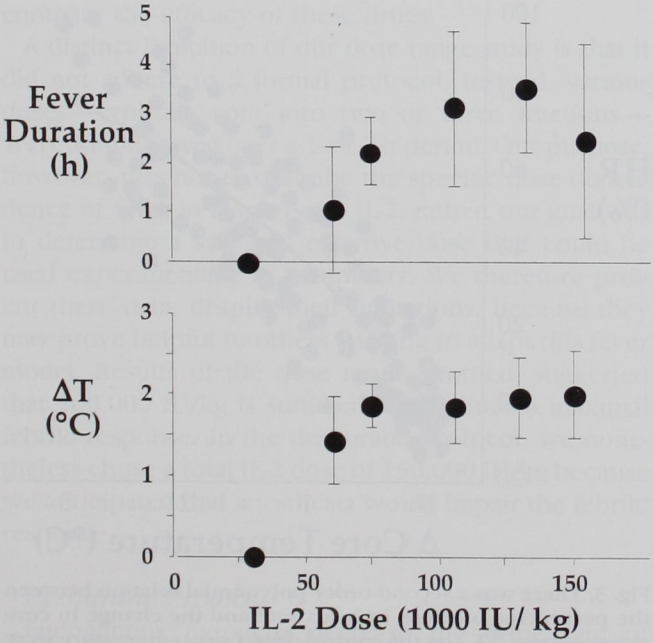

Fig. 1. The maximum change in core temperature and the duration of fever exceeding 38°C increased to a total dose of 100,000 IU/kg but subsequently failed to increase further. At that dose, fever magnitude was 1.8 ± 0.5°C, and the duration was 3.1 ± 2.0 h. Data are presented as the mean ± SD.

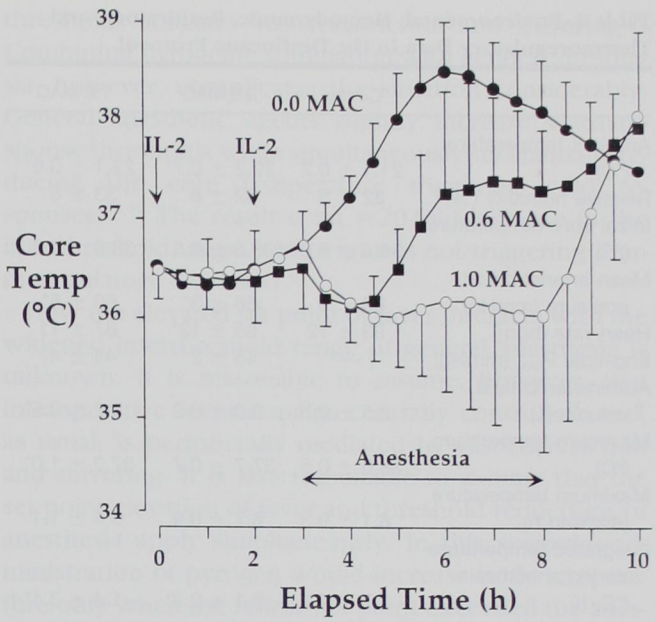

Fig. 2. Change in core temperature after administration of 50,000 IU/kg of interleukin (IL)-2 followed by a second dose of 100,000 IU/kg 2 h later. The first dose of IL-2 defined elapsed time 0 h; anesthesia was started after 3 elapsed h and continued for 5 h. Data are presented as the mean ± SD. Core temperatures during 0.6 MAC and 1.0 MAC desflurane differed significantly from the control day between 3.5 and 7.5 elapsed hours; temperatures during 1.0 MAC differed significantly from 0.6 MAC from 5.5–8.5 elapsed hours.

Desflurane Protocol

Peak core temperatures developed 5–8 h after administration of IL-2, times that did not differ significantly on the 3 study days (fig. 2). Shivering most frequently accompanied 0.6 MAC isoflurane (87.5%). It started with vasoconstriction, or soon thereafter, and lasted 15–60 min. Shivering was effective, usually increasing core temperature 0.02–0.03°C/min.

Desflurane reduced the integrated febrile response to pyrogen, from 7.7 ± 2.0°C·h on the control day, to 2.1 ± 2.3°C·h during 0.6 MAC, and to −1.4 ± 3.1°C·h during 1.0 MAC desflurane-induced anesthesia. Half of

Table 2. Environmental, Hemodynamic, Respiratory, and Thermoregulatory Data in the Desflurane Protocol

	Control	0.6 MAC	1.0 MAC
Ambient temperature (°C)	21.1 ± 0.2	22.2 ± 0.7*	22.1 ± 0.6*
Relative humidity (%)	32 ± 5	32 ± 8	33 ± 6
Initial core temperature (°C)	36.4 ± 0.3	36.5 ± 0.3	36.6 ± 0.3
Mean arterial blood pressure (mmHg)	83 ± 9	66 ± 3*	60 ± 6*
Heart rate (bpm)	93 ± 12	85 ± 12*	87 ± 11
End-tidal P_{CO_2} (mmHg)	—	45 ± 2	44 ± 4
Administered fluid volume (L)	2.5 ± 0.5	3.0 ± 0.2	3.2 ± 0.5*
Maximum temperature (°C)	38.6 ± 0.5	37.7 ± 0.7	37.2 ± 1.0*
Maximum temperature (elapsed h)	6.1 ± 0.3	6.7 ± 0.9	6.4 ± 1.1
Integrated temperature during anesthesia (°C · h)	7.7 ± 2.0	2.1 ± 2.3*	−1.4 ± 3.1*†
Mean skin temperature during anesthesia (°C)	34.6 ± 1.1	34.1 ± 0.9	33.7 ± 0.5*
Shivering (%)	62.5	87.5	25

Maximum temperature and the time to maximum temperature at 1.0 MAC were calculated using an n of 4 because half the volunteers became progressively hypothermic throughout anesthesia. Data are presented as mean ± SD.

* Statistically significant differences from control.

† Statistically significant difference from 0.6 MAC.

the volunteers remained vasodilated and became progressively hypothermic during anesthesia with 1.0 MAC desflurane. Their data were excluded from the analysis of peak temperature and time to peak temperature. In contrast, the other four experienced vasoconstriction and their core temperatures increased. Desflurane decreased the peak febrile response in a dose-dependent fashion, from 38.6 ± 0.5°C on the control day, to 37.7 ± 0.7°C during 0.6 MAC, and to 37.2 ± 1.0°C (n = 4) during 1.0 MAC (table 2). Core temperature elevations were invariably associated with fingertip vasoconstriction and often with shivering.

There was a second-order polynomial relation between the percent increase in heart rate and the change in core temperature on the control days. Core temperatures were compared with the mean values during the first elapsed hour. Change in heart rate was equal to $1.2 + 39 \cdot (\Delta T_c) - 4.5(\Delta T_c)^2$, where ΔT_c represents core temperature change, and $r^2 = 0.77$ (fig. 3). The volunteers remained hemodynamically stable throughout the protocol, and there were no serious complications. Three of the volunteers vomited during the study, one had diarrhea after 1 study day, and one reported a nightmare the evening after a study. Typically, however, the volunteers recovered quickly and were fit for discharge 3–4 h after emergence from anesthesia.

Discussion

Dose Range Protocol

The initial α plasma half-life of IL-2 is only ≈5–7 min; however, this is followed by a β half-life lasting 30–60 min. As a result, IL-2 is undetectable in plasma 4–8 h after bolus administration of 100,000 IU/kg. Fever onset was nonetheless delayed 2–4 h after administration of IL-2 in our volunteers. This long latency is consistent with clinical experience[30,31] and with the mechanism of action of the drug, which requires release of other primary pyrogens from macrophages.[23,24]

High doses of pyrogen produce biphasic fever in ani-

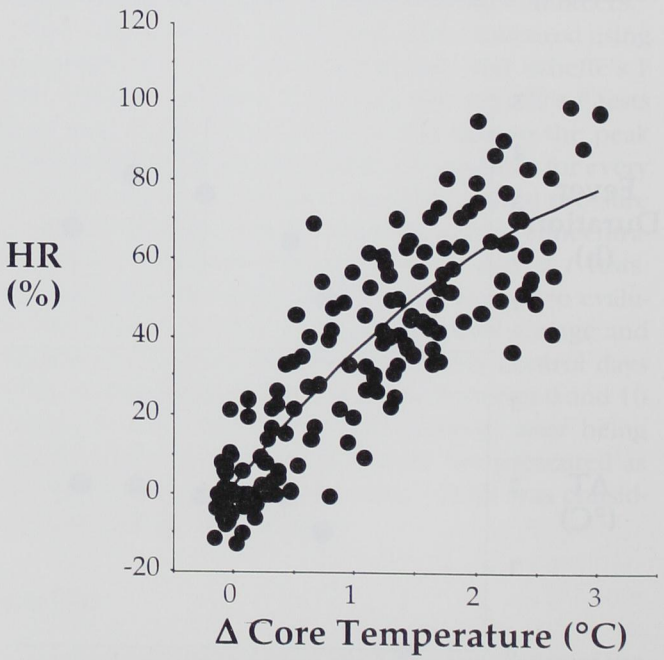

Fig. 3. There was a second-order polynomial relation between the percentage increase in heart rate and the change in core temperature (ΔT_c) on the control days. Core temperature were compared with the mean values during the first elapsed hour. Change in heart rate was equal to $1.2 + 39 \cdot (\Delta T_c) - 4.5 \cdot (\Delta T_c)^2$, and $r^2 = 0.77$. All values between 0 and 10 elapsed h were included in this analysis after being averaged into 30-min blocks.

mals.[32] The first phase appears to be a classical fever mediated by an elevated "set point." The second phase, in contrast, seems to be associated with sepsis syndrome and widening of the interthreshold range (temperatures not triggering thermoregulatory defenses) and is in part mediated by opioids.[33] Fever in our volunteers was strictly monophasic and was thus presumably a classical set point elevation. Our observation of universal vasoconstriction and frequent shivering are consistent with this interpretation.

Toxicity was minimal at every dose of IL-2 we tested, as would be expected from clinical experience.[19,34] A total dose of 100,000 IU/kg produced maximal magnitude and duration of fever. For general experimental use in unanesthetized volunteers, 100,000 IU/kg therefore seems preferable to higher doses, which are more likely to provoke complications. We failed to observe any evidence of tolerance or progressive toxicity. It therefore appears that volunteers can be evaluated on several occasions (suitably separated), with each being given several treatments or doses. Potential uses for this model include evaluation of the effects of opioids, sedatives, and regional anesthesia on the febrile response to pyrogenic stimulation. It may be especially helpful, however, for evaluation of antipyretic medications, because there is currently no easy way to quantify and compare the efficacy of these drugs.

A distinct limitation of our dose range study is that it did not adhere to a formal protocol. Instead, various doses—typically split into two or three fractions—were administered over a 1- or 2-h period. Our purpose, however, was not to describe the specific dose dependence of fever in response to IL-2; rather, our goal was to determine a safe and effective dose that could be used experimentally in volunteers. We therefore present these data, despite their limitations, because they may prove helpful to others wishing to adapt this fever model. Results of the dose range protocol suggested that 100,000 IU/kg is sufficient to produce a maximal febrile response. In the desflurane protocol, we nonetheless chose a total IL-2 dose of 150,000 IU/kg because we anticipated that anesthesia would impair the febrile response.

Desflurane Protocol

Endogenous pyrogens decrease the firing rate of warm-sensitive hypothalamic neurons, which synchronously increases thermoregulatory response thresholds.[35–37] Elevation in body temperature results when the disparity between febrile and normal cold-response thresholds activates vasoconstriction and shivering.[38] Combining pyrogenic stimulation with general anesthesia, however, complicates the situation considerably. General anesthetic agents slightly increase warm-response thresholds while simultaneously substantially reducing the core temperature triggering cold responses.[39,40] The result is an ≈20-fold increase in the interthreshold range (temperatures not triggering thermoregulatory defenses).[13]

How the elevated set point of fever interacts with the widened interthreshold range of general anesthesia is unknown. It is reasonable to assume, however, that intraoperative fever remains centrally controlled, and, as usual, is peripherally mediated by vasoconstriction and shivering. It is also reasonable to assume that the set point elevation of fever and threshold reductions of anesthesia apply simultaneously. In this scenario, administration of pyrogen would increase body temperature only when the febrile set point exceeded the anesthetic-induced reduction in the vasoconstriction and shivering thresholds.

The general anesthetic agent we used, desflurane, decreases the vasoconstriction and shivering thresholds ≈1.3°C at 0.5 MAC but decreases the thresholds >3°C at 0.8 MAC.[39] Administration of IL-2 without anesthesia increased core temperature ≈2.2°C. This increase was associated with vasoconstriction and shivering, indicating that it resulted specifically from an elevation in cold-response thresholds. The combination of 0.5 MAC desflurane with pyrogen might therefore be expected to produce ≈2.2°C (control increase) minus 1.3°C (anesthetic-induced threshold reduction), *i.e.*, ≈0.9°C. The observed 0.9°C difference between the control and 0.6 MAC days is therefore very approximately consistent with this prediction. In contrast, fever would not be anticipated at the higher anesthetic concentration because 1.0 MAC desflurane decreases cold-response thresholds far more than IL-2 increases the set point. Again consistent with this theory, fever was absent at the higher anesthetic concentration.

Our data therefore indicate that desflurane-induced anesthesia markedly impairs the febrile response to pyrogen administration, possibly by a central mechanism. An alternative explanation is inhibition of peripheral fever mediators. Consistent with this theory is the observation that urethan markedly reduces concentrations of tumor necrosis factor α in plasma.[41] It is likely that this inhibition contributes to the relative rarity of intraoperative fever. Fever is often a helpful sign, alerting clinicians to a variety of infectious and noninfectious

problems. Our data, however, suggest that the response to even substantial amounts of pyrogen may be limited or absent in anesthetized patients. Further, our volunteers were unparalyzed and frequently shivered; it is likely that paralysis would further reduce intraoperative fever.

Fever was consistently associated with tachycardia. Increasing heart rate during fever may relate to the change of metabolic rate resulting from increased voluntary muscle activity and shivering. Many studies show that the peripheral intravenous injection of pyrogens increases blood pressure and heart rate.[42,43] Intravenous infusion of high doses of pyrogens increases catecholamine levels in plasma. It remains unclear, however, whether pyrogen-induced increases in catecholamines mediate tachycardia.[44] An additional potential explanation is that fever augments the rate of many metabolic reactions, thus increasing systemic metabolic rate.[12]

Our study evaluated fever after administration of pyrogen, which is arguably the most clinically relevant aspect of the response. From a thermoregulatory point of view, however, it would be helpful to determine the thresholds for the major thermoregulatory defenses. These data would provide a better understanding of how the set point elevation of fever combines with anesthetic-induced expansion of the interthreshold range to reduce the febrile response to pyrogenic stimulation during anesthesia. Threshold determinations require deliberate manipulations of core or skin temperature, however; consequently these data could not be acquired in the course of the current protocol.

A limitation of our study is that ambient temperature was significantly lower on the control day. The difference, however, was only $\approx 1°C$, which would increase passive heat loss $<10\%$. Fever, however, is a regulated hyperthermia. It is therefore unlikely that core temperatures on the control day would have been much greater at a slightly higher ambient temperature. Administration of desflurane reduced mean arterial blood pressure and heart rate; similarly, more intravenous fluid was required during anesthesia. These are expected consequences of general anesthesia, however.

Summary

A total dose of 100,000 IU/kg of IL-2 produced maximal magnitude ($1.8 \pm 0.5°C$) and duration (3 ± 2 h) of fever in unanesthetized volunteers. We failed to observe tolerance or any important toxicity. These data therefore suggest that 100,000 IU/kg is suitable for general experimental use, such as testing the efficacy of antipyretic medications. Desflurane reduced the integrated febrile response and peak core temperature in response to administration of IL-2 in a dose-dependent manner. Anesthetic-induced inhibition of febrile responses therefore contributes to the relative rarity of fever during surgery.

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