The Effect of Pyrogen Administration on Sweating and Vasoconstriction Thresholds during Desflurane Anesthesia

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**Background:** General anesthetics increase the sweating-vasoconstriction interthreshold range (temperatures not triggering thermoregulatory defenses), whereas fever is believed to

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only increase the setpoint (target core temperature). However, no data characterize thresholds (temperatures triggering thermoregulatory defenses) during combined anesthesia and fever. Most likely, the combination produces an expanded interthreshold range around an elevated setpoint. The authors therefore tested the hypothesis that thermoregulatory response thresholds during the combination of fever and anesthesia are simply the linear combination of the thresholds resulting from each intervention alone.

**Methods:** The authors studied eight healthy male volunteers. Fever was induced on the appropriate days by intravenous injection of 30 IU/g human recombinant interleukin 2 (IL-2), followed 2 h later by an additional 70 IU/g. General anesthesia consisted of desflurane 0.6 minimum alveolar concentration (MAC). The volunteers were randomly assigned to the following groups: (1) control (no desflurane, no IL-2); (2) IL-2 alone; (3) desflurane alone; and (4) desflurane plus IL-2. During the fever plateau, volunteers were warmed until sweating was observed and then cooled to vasoconstriction. Sweating was evaluated from a ventilated capsule and vasoconstriction was quantified by volume plethysmography. The tympanic membrane temperatures triggering significant sweating and vasoconstriction identified the respective response thresholds. Data are presented as the mean ± SD; P < 0.05 was considered significant.

**Results:** The interthreshold range was near 0.4°C on both the control day and during IL-2 administration alone. On the IL-2 alone day, however, the interthreshold range was shifted to higher temperatures. The interthreshold range increased significantly during desflurane anesthesia to 1.9 ± 0.6°C. The interthreshold range during the combination of desflurane and IL-2 was 1.2 ± 0.6°C, which was significantly greater than on the control and IL-2 alone days. However, it was also significantly less than during desflurane alone.

**Conclusion:** The combination of desflurane and IL-2 caused less thermoregulatory inhibition than would be expected based on the effects of either treatment alone. Fever-induced activation of the sympathetic nervous system may contribute by compensating for a fraction of the anesthetic-induced thermoregulatory impairment. (Key words: Fever; hyperthermia; interleukin 2; temperature; thermoregulation.)

MOST perioperative temperature changes result from alterations in thermoregulatory control. Thermoregulatory responses can be characterized by thresholds,
which are defined as the core temperatures (at a designated skin temperature) that trigger defenses against excessive heat or cold, such as sweating or vasoconstriction. The difference between the sweating and the vasoconstriction thresholds defines the interthreshold range; these temperatures do not trigger thermoregulatory defenses.\(^1\) The interthreshold range is distinctly non-zero. But because it is normally only a few tenths of a degree centigrade,\(^2\) it is sometimes approximated as a setpoint (target core temperature).

The effects of anesthesia and sedatives on thermoregulatory responses are fairly well-established. Volatile anesthetics,\(^3\) propofol,\(^4\) opioids,\(^5,6\) and sedatives\(^7,8\) slightly increase the sweating threshold while markedly decreasing the vasoconstriction and shivering thresholds. The result is that the sweating-to-vasoconstriction interthreshold range increases from a few tenths of a degree to 2–4°C, depending on drug type and dose.

Fever is a regulated hyperthermia, mediated by endogenous pyrogens, especially interleukin 1 (IL-1), interleukin 6, tumor necrosis factor α (TNF-α), and interferon α.\(^9,10\) The precision of thermoregulatory control remains normal during fever in rabbits, but is centered around an elevated temperature.\(^11\) This synchronous elevation in the cold- and warm-response thresholds can be considered a setpoint increase. Fever in humans is similarly believed to increase the setpoint, although the interthreshold range has yet to be reported in febrile humans.

Fever can occur during anesthesia in response to infectious or noninfectious causes. However, intraoperative fever is relatively rare, considering how often pyrogenic causes are likely to be present during surgery, and how common fever is postoperatively. Consistent with this observation, even low concentrations of desflurane markedly inhibit manifestation of fever.\(^12\) Opioids also inhibit fever, although to a lesser extent; this inhibition appears to be centrally mediated because plasma cytokine concentrations during fever are comparable with and without opioids.\(^13\)

General anesthetics and sedatives thus increase the interthreshold range, whereas fever is believed to increase the setpoint without decreasing precision of thermoregulatory control. However, there are currently no data characterizing the effects of a combined anesthetic-induced increase in the interthreshold range with fever-induced setpoint elevation. The most likely scenario is that the two effects occur simultaneously; that is, the combination of general anesthesia and fever simply produces an expanded interthreshold range around an elevated setpoint.

Accordingly, we tested the hypothesis that when fever is induced during desflurane anesthesia (1) the sweating threshold is increased and the vasoconstriction threshold is decreased, compared to fever alone, just as it is during anesthesia alone; and (2) the expanded interthreshold range is centered around a setpoint that is elevated to the same extent as during fever alone. In other words, we postulate that thermoregulatory response thresholds during the combination of fever and anesthesia will simply be the linear combination of the thresholds resulting from each intervention alone.

Evaluating the independent and combined effects of fever and volatile anesthetics on thermoregulatory response thresholds is the first step in identifying the mechanism by which anesthesia inhibits manifestation of fever. However, this issue has only been addressed once previously; in that case, urethane anesthesia was shown to reduce peripheral concentrations of TNF-α in rats.\(^14\) We therefore also tested the hypothesis that peripheral inhibition of cytokine production contributes to anesthetic-induced inhibition of fever.

### Methods

With approval of the Committee on Human Research at the University of California, San Francisco, we studied eight men volunteers. Morphometric characteristics included age (27 ± 3 yr), height (176 ± 2 cm), and weight (76 ± 9 kg). The percentage of body fat was 19 ± 6, as determined by infrared interactance (Futrex, Inc., Harford, MD). None of the patients were obese, were taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud syndrome.

#### Treatment Protocol

Each volunteer participated on six study days. To control for circadian rhythms, study days started at 8:00 AM, when fever was induced. In contrast, the study began at 12:00 PM, when anesthesia alone was given and at 2:00 PM on the control day; the relevant thermoregulatory responses thus occurred at similar times on each study day. The volunteers fasted 8 h before arriving at the laboratory and were not given any premedication. They
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rested in the supine position on a standard operating room table and were minimally clothed; ambient temperature was maintained near 22°C.

On the first day (fever pattern day), the febrile response to interleukin-2 (IL-2) administration was determined. A catheter was inserted in a left forearm vein. An additional catheter was inserted in a right antecubital vein for blood sampling. Lactated Ringer's solution at ambient temperature was infused at approximately 300 ml/h. Fever was induced by intravenous injection of 30 IU/g human recombinant IL-2 at elapsed time zero, followed 2 h later by 70 IU/g of the drug (Chiron, Inc., Berkeley, CA). This dose and timing was adapted from our previous fever study. The individual times at which maximum fever was observed was then considered the target time for determination of thermoregulatory response thresholds on subsequent study days. Thresholds were thus determined near the peak thermoregulatory effect of IL-2 in each volunteer.

Treatments on the subsequent five study days consisted of a control day, and various combinations of pyrogen (IL-2) and desflurane anesthesia. Pyrogen was administered using the protocol above. Anesthesia started 1 h after the second dose of IL-2 and was induced with propofol (5 mg/kg), and a laryngeal mask was inserted. Anesthesia was subsequently maintained with desflurane 0.6 minimum alveolar concentration (MAC) in oxygen and nitrogen. The volunteers breathed spontaneously, but ventilation was assisted when necessary to maintain end-tidal partial pressure of carbon dioxide (P_{CO2}) near 45 mmHg because hypercapnia may influence thermoregulatory responses. Inspired oxygen was normally near 30% (in nitrogen), but was increased as necessary to maintain the hemoglobin oxygen saturation at more than 95%. Anesthesia continued until the appropriate thresholds were obtained; the duration of anesthesia thus differed somewhat for each participant.

The specific treatments, which were randomly assigned, included (1) control (no desflurane, no IL-2); (2) Desflurane alone; (3) IL-2 alone; (4) desflurane plus IL-2 (warming); and (5) desflurane plus IL-2 (cooling). The desflurane plus IL-2 treatment was split into separate warming and cooling days because it would otherwise have been impossible to determine both the sweating and the vasoconstriction thresholds (see Measurements) near the target time. Therefore, only the sweating threshold was determined on the desflurane plus IL-2 (warming) day and only the vasoconstriction threshold was determined on the desflurane plus IL-2 (cooling) day (fig. 1).

Thermal Management
Core and skin temperature changes were restricted to 2°C/h or less because this rate does not trigger dynamic thermoregulatory responses. Throughout the protocol, arms were protected from active warming and cooling to avoid locally mediated vasoconstriction. However, all other skin below the neck was similarly manipulated.

On the control and desflurane alone days, skin and core temperatures were first gradually increased with a forced-air warmer (Augustine Medical, Inc., Eden Prairie, MN) and circulating-water mattress (Cincinnati Sub-Zero, Cincinnati, OH) until significant sweating was detected (see Measurements). Skin and core temperatures were then gradually decreased, using the circulating-water mattress and a prototype forced-air cooler from Augustine Medical, Inc., until vasoconstriction was observed (below). On the IL-2 alone and the desflurane plus IL-2 days, cutaneous warming and cooling was initiated as necessary to trigger the sweating or vasoconstriction thresholds, or both, near the target time. Each study day ended when the appropriate thresholds were detected.

Measurements
Core temperature was recorded from the tympanic membrane using Mon-a-Therm thermocouples (Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO). 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 aural canal was occluded with cotton, the probe securely taped in place, and a gauze bandage was positioned over the external ear.

Mean skin surface temperature was calculated from measurements at 15 area-weighted sites. Temperatures were recorded at 1-min intervals from thermocouples connected to calibrated Iso-Thermex thermometers (Columbus Instruments, Corp., Columbus, OH) having an accuracy of 0.1°C and a precision of 0.01°C.

Sweating was continuously recorded from the left-upper part of the chest using a ventilated capsule. We considered a sustained sweating rate exceeding 40 g · m^{-2} · h^{-1} significant. Absolute right-hand, middle fingertip blood flow was quantified by venous-occlusion volume plethysmography at 5-min intervals. A sustained decrease in fingertip blood flow to less than 0.25 ml/min identified significant vasoconstriction.

Peripheral venous blood was sampled at hourly intervals on the desflurane alone day, IL-2 alone day, and

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desflurane plus IL-2 (warming) day. The samples were centrifuged at 300g for 20 min; the plasma was then separated and stored at −30°C until assay. The biological activity of IL-2 was determined by an immunoenzymatic assay (IL-2 EASIA; Biosource Europe S.A., Fleurus, Belgium). Plasma interleukin-6 (IL-6) concentrations were measured by an enzyme-linked immunosorbent assay (Human Interleukin-6 ELISA Kit; Toray Industries, Inc., Tokyo, Japan). TNF concentrations were determined by a human immunoassay (Quantikine HS; R&D Systems, Minneapolis, MN). Plasma interleukin-10 (IL-10) concentrations were determined by a solid-phase enzyme-amplified immunoassay (IL10 EASIA Kit; Medgenix Diagnostics S.A., Fleurus, Belgium). Interleukin-8 (IL-8) in plasma was measured using the Human IL8 detection kit (Fujirebio Inc., Tokyo, Japan) using an enzyme-linked immunosorbent assay. Interleukin-1 receptor antagonist (IL-1ra) in plasma was measured by MEDGENIX IL1ra EASIA kit (BioSource Europe S.A.) In each case, the assays were performed per the manufacturer directions, and appropriate calibration curves were constructed. All are highly specific and sensitive over the range of observed values.

Most of these cytokines are considered proinflammatory. However, IL-10 is antiinflammatory, as is IL-1ra. Administration of IL-2 provokes expression and release of IL-1β, TNF, and various other proinflammatory cytokines. High concentrations of IL-2 (100–1,000 U/ml) also induce IL-1 production in human mononuclear cell and large granular lymphocytes. It has, nonetheless, proven difficult to detect significant increases in IL-1β in the circulation of febrile animals. We have also had difficulty detecting this cytokine in our previous human studies. Accordingly, we measured IL-1ra, which is secreted by monocytes and macrophages and opposes the actions of IL-1α and IL-1β by binding to IL-1 receptors.

Heart rate and oxyhemoglobin saturation (SPO₂) were measured continuously using pulse oximetry; blood pressure was determined oscillometrically at 5-min intervals at the left ankle. End-tidal Pco₂ was measured from the laryngeal mask during anesthesia.

Data Analysis
The cutaneous contribution to sweating and to vasocclusion and shivering is linear. We therefore used...
measured skin and core temperatures in degrees Celsius at each threshold to calculate the core temperature threshold that would have been observed had skin been maintained at a single designated temperature. We previously described the derivation, validation, and limitations of this method. Briefly, we assumed that the thresholds for sweating and vasoconstriction are linear functions of skin and core temperatures, and that skin temperature contributes approximately 10% to sweating and approximately 20% to vasoconstriction. The designated skin temperature was set at 34°C, a typical intraoperative value.

Hemodynamic data, end-tidal P\textsubscript{\text{CO}}\textsubscript{2}, and ambient temperature at each threshold were averaged among volunteers. Results were compared with analysis of variance and the Fisher least significant difference tests. Likewise, cytokine concentrations were compared with analysis of variance and the Fisher least significant difference tests. Time-dependent changes were similarly evaluated. Data are presented as the mean ± SD; \(P < 0.05\) was considered statistically significant.

**Results**

Ambient temperatures were comparable on each of the study days. End-tidal P\textsubscript{\text{CO}}\textsubscript{2} and desflurane partial pressures on the anesthesia days also were similar. There were statistically significant differences in blood pressure among the study days. However, the differences were of modest magnitude. Heart rates on the IL-2 alone day and on the combination day differed significantly from control and the desflurane alone day by roughly 20% (table 1).

The sweating and vasoconstriction thresholds were 37.2 ± 0.3°C and 36.7 ± 0.3°C, respectively, on the control day. The thresholds increased significantly to 38.8 ± 0.6°C and 38.4 ± 0.8°C, respectively, during IL-2 alone. The sweating threshold during desflurane alone was 37.6 ± 0.3°C, whereas the vasoconstriction threshold was 35.7 ± 0.4°C. When IL-2 and desflurane were combined, the sweating and vasoconstriction thresholds were 39.1 ± 0.5°C and 37.9 ± 0.6°C, respectively (table 2, fig. 2).

The interthreshold ranges on the control day and during IL-2 alone did not differ significantly: 0.5 ± 0.5°C and 0.4 ± 0.4°C, respectively. The interthreshold range increased significantly during desflurane anesthesia to 1.9 ± 0.6°C. The interthreshold range during the combination of desflurane plus IL-2 was 1.2 ± 0.6°C, which was significantly greater than on the control and IL-2 alone days. However, it was also significantly less than during desflurane alone (table 2, fig. 2).

On the desflurane alone day, IL-2 concentration increased significantly to a peak of 12 ± 7 ng/ml after 5 elapsed h. Other cytokine concentrations remained at baseline values. In contrast, with IL-2 alone and with the combination of desflurane and IL-2, plasma IL-2 concentrations peaked after 3 elapsed h. Plasma concentration of IL-6, IL-10, TNF, and IL-8 increased later, reaching peak levels after 45 elapsed h. All the cytokines, except...
Table 2. Mean Skin and Core Temperatures, Calculated Thresholds, and Interthreshold Ranges

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Desflurane</th>
<th>IL-2</th>
<th>Desflurane and IL-2</th>
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<tr>
<td><strong>Sweating</strong></td>
<td></td>
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<tr>
<td>Mean skin</td>
<td>36.4 ± 0.5</td>
<td>37.1 ± 0.3</td>
<td>37.5 ± 0.4</td>
<td>38.3 ± 0.4</td>
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<tr>
<td>Core</td>
<td>36.9 ± 0.3</td>
<td>37.2 ± 0.3</td>
<td>38.3 ± 0.6</td>
<td>38.6 ± 0.5</td>
</tr>
<tr>
<td>Threshold</td>
<td>37.2 ± 0.3</td>
<td>37.6 ± 0.3</td>
<td>38.7 ± 0.6†</td>
<td>39.1 ± 0.5†</td>
</tr>
<tr>
<td><strong>Vasoconstriction</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean skin</td>
<td>32.7 ± 1.6</td>
<td>31.9 ± 0.9</td>
<td>35.2 ± 1.6</td>
<td>34.5 ± 1.7</td>
</tr>
<tr>
<td>Core</td>
<td>36.9 ± 0.1</td>
<td>36.1 ± 0.3</td>
<td>38.1 ± 0.5</td>
<td>38.0 ± 0.8</td>
</tr>
<tr>
<td>Threshold</td>
<td>36.7 ± 0.3</td>
<td>35.7 ± 0.4†</td>
<td>38.3 ± 0.8*</td>
<td>37.9 ± 0.5†</td>
</tr>
<tr>
<td><strong>Interthreshold range</strong></td>
<td>0.5 ± 0.5</td>
<td>1.9 ± 0.6†</td>
<td>0.4 ± 0.4*</td>
<td>1.2 ± 0.6††</td>
</tr>
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</table>

Thresholds were calculated at a designated skin temperature of 34°C. The interthreshold range is the difference between the sweating and vasoconstriction thresholds. All temperatures are reported as mean ± SD in °C. Statistical analysis was restricted to the thresholds and interthreshold range.

* Significantly different from control.
† Significantly different from desflurane alone.
‡ Significantly different from IL-2 alone.

IL-6, subsequently decreased to near-baseline values by 78 elapsed h. IL-6 decreased, but remained above baseline throughout the study period. There were no statistically significant or clinically important differences in the cytokine concentrations on the IL-2 alone and the IL-2 plus desflurane days (fig. 3).

Discussion

Fever is believed to increase the setpoint without decreasing precision of thermoregulatory control. In our study, the sweating threshold on the fever alone day was raised 1.6°C and the vasoconstriction thresholds increased 1.7°C compared to the control day. However, the sweating-to-vasoconstriction interthreshold range did not change significantly, the difference being only 0.1°C. Our data thus suggest that fever synchronously augments thermoregulatory thresholds without a change in interthreshold range and can therefore be considered an increase in the setpoint.

During desflurane anesthesia, sweating thresholds are increased and vasoconstriction thresholds are decreased, thereby widening the interthreshold range threefold to 20-fold. Our data confirmed these results by demonstrating an almost fourfold increase in the interthreshold range to 1.9°C. The combination of IL-2 administration and desflurane anesthesia increased the sweating threshold 0.3°C and reduced the vasoconstriction threshold 0.4°C compared to fever alone. Consequently, the interthreshold range increased to 1.2°C.

The interthreshold range was thus significantly less during the combination of IL-2 and desflurane than during desflurane alone. These data disprove our primary hypothesis that thermoregulatory response thresholds during the combination of fever and anesthesia are a simple linear combination of the thresholds resulting from each intervention alone. Confirming our hypothesis would have suggested that the thermoregulatory effects of combining fever with various anesthetics and sedatives could be predicted from the well-established effects of these drugs on response thresholds.
Elapsed Time (h)

Fig. 3. Plasma concentrations of interleukin-1 receptor antagonist (IL-1ra), interleukin 6 (IL-6), interleukin 2 (IL-2), interleukin 10 (IL-10), interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α). Zero indicates administration of the first IL-2 dose. During desflurane alone (diamonds), cytokine concentrations were only measured just before and during the first 5 h of the anesthesia period. The first dose of IL-2 was given at elapsed time zero; desflurane anesthesia lasted from 3 h to 8 h elapsed. Concentrations of IL-1ra, IL-6, IL-2, IL-10, IL-8, and TNF all increased significantly over time. The values with IL-2 alone (squares) and the combination of IL-2 and desflurane (triangles) differed significantly from desflurane alone. Some error bars were omitted for clarity; their dimensions are similar to those shown.

However, our data indicate that the thermoregulatory effects of combining fever with different types of anesthetics cannot be predicted from existing knowledge.

A potential explanation for this curious result would be anesthetic-induced inhibition of peripheral cytokine release, as has been observed in rats anesthetized with urethane.16 Our data, however, also fail to confirm that theory: there were no statistically significant differences in circulating cytokine concentrations during IL-2 alone and the combination of IL-2 and desflurane. We are therefore forced to reject our secondary hypothesis.

There is no obvious explanation why the combination of IL-2 and desflurane produce less inhibition than might be expected from the responses observed with IL-2 alone or desflurane alone. One possibility, however, is that fever activates the sympathetic nervous system.52 This theory is supported by a significant increase of heart rates on the combined and fever alone days as compared to control and desflurane alone days. In addition, we previously demonstrated that the vasoconstriction threshold during enflurane anesthesia is elevated (i.e., less thermoregulatory inhibition) during painful stimulation.53 Furthermore, vasoconstriction thresholds during nitrous oxide administration—a drug that activates the sympathetic nervous system—are higher than during comparable MAC fractions of sevoflurane or isoflurane.54 Therefore, it may be that activation of the sympathetic nervous system by fever to some extent compensates for anesthetic-induced inhibition, the result being less inhibition than might otherwise be expected when the two factors are combined.

The major limitation of our study is that IL-2, administered as we did, produced a fever plateau that usually only lasted approximately 1.5 h. (Numerous preliminary studies failed to identify a dosing regimen that produced any better fever plateau.) We were therefore obligated to test each study condition on a separate day, and even needed two days to evaluate the sweating and vasoconstriction thresholds during the combination of IL-2 and desflurane. The design was further complicated because the plateau did not necessarily occur at the same time in different volunteers. Fortunately, however, the plateau occurred at the same time in each volunteer on different study days and there was no evidence whatsoever that the volunteers developed tolerance to the effects of cytokine administration. We were thus able to determine the plateau time and duration in each volunteer in a preliminary study and then time the remaining study days optimally.

An additional limitation is that we arithmetically compensated for skin temperature perturbations to calculate core temperature thresholds at a constant designated skin temperature. The coefficient (β) relating skin and core contributions to thermoregulatory control is well-established in unanesthetized men and women.28,29 Unpublished data indicate that β remains unchanged during anesthesia, but β certainly has not been evaluated during fever or the combination of anesthesia and fever. To the extent that β varies during these circumstances, our calculated thresholds may be in error.

In summary, IL-2 synchronously augmented the vasoconstriction and sweating thresholds. The interthreshold range thus remained constant near 0.4°C, this pattern is consistent with an elevated setpoint during fever. In contrast, desflurane alone increased the sweating threshold while simultaneously reducing the vasoconstriction threshold. The result was a fourfold increase in the interthreshold range to 1.9°C. Curiously, pyrogenic stim-
ulation combined with desflurane anesthesia increased the interthreshold range only to 1.2°C. It remains unknown why the combination of desflurane and IL-2 causes less thermoregulatory inhibition than would be expected based on the effects of either treatment alone. However, fever-induced activation of the sympathetic nervous system may contribute by compensating for a fraction of the anesthetic-induced thermoregulatory impairment.

Finally, there were no statistically significant differences in circulating cytokine concentrations during IL-2 alone and the combination of IL-2. These data do not support the theory that anesthetic-induced inhibition of peripheral cytokine release contributes to anesthetic-induced inhibition of fever.

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