Fever during anaesthesia

Chiharu Negishi*
Assistant Professor
Department of Anaesthesia, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku,
Tokyo 162-8666, Japan

Rainer Lenhardt
Assistant Director, Assistant Professor
Outcomes Research Institute, Department of Anesthesiology, University of Louisville, 501 East Broadway,
Suite 210, Louisville, KY 40202, USA

Fever occurs when pyrogenic stimulation activates thermal control centres. Fever is common
during the perioperative period, but rare during anaesthesia. Although only a limited number of
studies are available to explain how anaesthesia affects fever, general anaesthesia seems to inhibit
fever by decreasing the thermoregulatory-response thresholds to cold. Opioids also inhibit fever;
however, the effect is slightly less than that of general anaesthesia. In contrast, epidural
anaesthesia does not affect fever. This suggests that hyperthermia, which is often associated with
epidural infusions during labour or in the post-operative period, may be a true fever caused by
inflammatory activation. Accordingly, this fever might be diminished in patients who receive
opioids for pain treatment. Post-operative fever is a normal thermoregulatory response usually of
non-infectious aetiology. Fever may be important in the host defence mechanisms and should not
be routinely treated lest the associated risks exceed the benefits.

Key words: fever; anaesthesia; volatile anaesthetics; intravenous anaesthetics; opioids; epidural
analgesia; temperature; thermoregulation; thermoregulatory threshold; inflammation; cytokines;
pyrogen; antipyretic; treatment of fever.

FEVER

Normal thermoregulatory control and fever

Thermoregulatory responses can be characterized by thresholds, which are defined as
the core temperatures (at a designated skin temperature) that trigger physiological
defences against excessive heat or cold. The difference between the sweating and
vasoconstriction thresholds defines the inter-threshold range; temperatures within this
range do not trigger thermoregulatory defences. The inter-threshold range, which is
normally only a few tenths of a degree centigrade, is sometimes approximated as a single target core temperature (setpoint).

Fever is a regulated increase in body temperature. It develops when pyrogenic stimulation activates hypothalamic thermoregulatory control centres. During fever, the setpoint increases and there is a synchronous elevation in the cold-response and warm-response thresholds, i.e. heat loss and heat production are regulated to a higher temperature. The precision of thermoregulatory control remains normal, and the inter-threshold range is similar to that of normothermic individuals. (Figure 1).

Passive hyperthermia is also an increase in body temperature but a distinct entity in which the thermoregulatory setpoint is normal. Passive hyperthermia is a condition that develops when heat production by the body exceeds heat loss.

During general anaesthesia, most patients become hypothermic. However, hyperthermia occurs at relatively high incidence during anaesthesia in paediatric patients, in patients with brain stroke or injury or acute peritonitis, or in patients undergoing otolaryngeal surgery. It is not always easy to distinguish fever from passive hyperthermia during general anaesthesia. However, fever is likely to be accompanied by vasoconstriction and shivering at emergence of anaesthesia or in the post-anaesthesia care unit.

Role of fever

For millennia, fever has been considered a protective response to combat infection, and it has provided a useful warning to clinicians. Recently, it has been increasingly realized that fever is one part of a complex host defence response to infection or non-infectious diseases. The benefit of the increase in body
temperature on host defence is not entirely clear. Several animal studies have examined the effect of temperature on the mortality rate during bacterial infection. Kluger et al. demonstrated the effect of elevated body temperature on survival rate of the desert iguana (*Dipsosaurus dorsalis*) infected with bacteria (*Aeromonas hydrophila*). They showed a clear correlation between the increase in body temperature following bacterial infection and the host survival rate. In another study, Vaughum et al. demonstrated the effect of fever on the survival rate of infected rabbits. They showed that antipyretic use reduced body temperature and significantly decreased the host survival rate. Temperature modulation to the higher setpoint during infection is also observed in fish, which suggests that fever is an adaptive response in numerous species.

Although fever may be beneficial for infected patients, the associated symptoms, such as increasing cardiac output, oxygen consumption, and energy consumption, are sometimes harmful. In such cases, antipyretic use needs to be considered, especially for the elderly or patients with poor cardiac or pulmonary function.

**Process of fever**

Normally, thermoregulatory control is principally neuronally mediated. However, during fever, humoral mediators such as endogenous pyrogens play important roles in the control of body temperature. The major endogenous pyrogens include interleukin-1, interleukin-6, tumour necrosis factor (TNF-alpha), and interferon-alpha. The other factors, including macrophage inflammatory protein, also contribute. The entire molecular aspect of how these endogenous cytokines send signals to the brain to induce prostaglandin (PG) E2, the final mediator of fever, is not completely known. However, in addition to this humoral mechanism, vagal afferent signals seem to be another important pathway for induction of fever.

Once fever is induced, the core target temperature is set at a higher temperature. That is, all thermoregulatory response thresholds (core temperatures triggering responses) occur at higher temperatures. As a result, cold-defences such as vasoconstriction and shivering are strongly augmented in the early stage of fever. During fever, the inter-threshold range is kept in the narrow range as in the normal condition. The maximal temperature usually does not exceed 42 °C.

Fever is just one part of an acute response to inflammation and, like other parts of the response, it is mediated by the immune, endocrine and neuronal systems. During the course of fever, various mediators are released that modulate it. The entire mechanism of inflammation is complex, and these mediators usually up-regulate and down-regulate each other. For example, endogenous pyrogens, which are pro-inflammatory cytokines, activate the release of endogenous antipyretics or cryogens that act to reduce fever. Interleukin-10, glucocorticoids, vasopressin, alpha-melanocyte-stimulating hormone (alpha-MSH), nitric oxide, and TNF-alpha in certain situations, all appear to be endogenous antipyretics. They may be acting to prevent body temperature from rising to dangerous levels, to decrease the setpoint after some period of fever, or both.

Adding to these endogenous mediators, many drugs administered during the perioperative period possess potentially immunomodulator effects. Antipyretics and steroids decrease fever by modifying the neuronal and adrenal axis. Sedatives and opioids seem to reduce fever by both central and peripheral mechanisms. In addition, surgical procedures and pre-operative examinations activate the immune...
system to some degree. Even though numerous clinical and basic studies have been done in the past, further investigations will be needed to understand the entire inflammatory response and the immunomodulator effect of drugs during the perioperative period.

Figure 2. Generation of fever. Exogenous pyrogens (LPS, endotoxin, etc.) and other pyrogenic stimulations induce pyrogenic cytokines (IL-1, TNF-alpha, IL-6). Circulating IL-6, which is induced by both IL-1 and TNF-alpha, is considered to be the key cytokine for inducing prostaglandin E2 (PGE2) in the central nervous system. PGE2 alters the firing rate of thermosensitive neurons in the anterior hypothalamus (setpoint elevation). The vagal afferent nerve and also the cutaneous sensory nerve seem to transport signals to induce fever. Especially in the later stage of fever, antipyretics and other factors, including AVP and alpha-MSH, are involved in attenuating fever. CNS = central nervous system; PGE2 = prostaglandin E2; AVP = arginine vasopressin; alpha-MSH = melanocyte stimulating hormone; IL-1 = interleukin-1; IL-6 = interleukin-6; TNF-alpha = tumour necrosis factor-alpha. Solid arrows indicate stimulus responses, and broken arrows indicate inhibitory responses. "TNF-alpha acts as an inhibitor of fever under certain circumstances."
Thermoregulatory control during anaesthesia

Most perioperative temperature changes result from alterations in thermoregulatory control. The effects of anaesthesia and sedatives on thermoregulatory responses are well established. Volatile anaesthetics, propofol, opioids and sedatives all slightly increase the sweating threshold while markedly decreasing the vasoconstriction and shivering thresholds.24–29 As a result, the sweating-to-vasoconstriction inter-threshold range, which is usually only a few tenths of a degree centigrade (°C), increases to a 2–4 °C range, depending on the drug and dose.1

Volatile anaesthesia and fever

Fever is relatively rare during general anaesthesia—especially considering how often pyrogenic aetiologies are likely to be present during the perioperative period. This suggests that general anaesthesia per se attenuates fever by the lowering of thermoregulatory thresholds of cold defences.

The effect of desflurane anaesthesia on fever has been evaluated using a human fever model in which fever was induced by intravenous administration of IL-2 to male volunteers.30 Desflurane anaesthesia produced a dose-dependent inhibition of IL-2-induced fever, with 1.0 MAC essentially obliterating the temperature increase (Figure 3). The results of this study may explain why fever is rare during general anaesthesia.

The mechanisms by which anaesthesia inhibits manifestation of fever are not completely understood. However, one possible mechanism is a central action of volatile anaesthetics.24 The other possibility is a peripherally mediated inhibition via reduced release of pyrogenic cytokines.31 To clarify the thermoregulatory effects of desflurane anaesthesia on fever, the thermoregulatory thresholds for sweating and vasoconstriction were determined with 0.6 MAC desflurane anaesthesia with fever
induced by IL-2. 3 The combination of IL-2 administration and desflurane anaesthesia increased the sweating threshold and reduced the vasoconstriction threshold compared to IL-2 alone. Consequently, the inter-threshold range increased; however, the range was significantly less than during desflurane anaesthesia alone. This effect is unclear, but one possibility is that fever-induced activation of the sympathetic nervous system compensates for a fraction of the anaesthetic-induced thermoregulatory impairment (Figure 4).

To evaluate the peripherally mediated inhibition by anaesthesia, plasma cytokine levels during desflurane anaesthesia combined with fever were measured in the same study. Desflurane did not affect the plasma concentration of the circulating cytokines induced by IL-2 administration (IL-1ra, IL-6, IL-8, IL-10, TNF-alpha). Thus, it appears that desflurane decreases the thermoregulatory thresholds of cold defences via a central action.

Although a central inhibitory mechanism appears to play an important role in anaesthesia-mediated suppression of fever, there is also evidence that anaesthetics are immunosuppressive as well. Recently, in vivo and in vitro studies demonstrated that both volatile and intravenous anaesthetics and opioids suppress cytokine production and activity. Roytblat et al demonstrated that, before cardiac pulmonary bypass, ketamine (0.25 mg/kg) reduces serum interleukin-6 (IL-6) concentration during and post surgery. In addition, alfentanil and propofol...
anaesthesia diminishes release of IL-6 during abdominal surgery compared with isoflurane anaesthesia. Plasma concentrations of IL-6 are associated with fever. These findings suggest that general anaesthesia, especially intravenous anaesthetics, also modulates fever by a peripheral mechanism, at least in part.

Intravenous anaesthetics and sedatives

The effects of intravenous anaesthetics on fever have not been formally reported. However, most anaesthetics and sedatives have similar effects on thermoregulatory control: they slightly increase the sweating threshold and markedly decrease the vasoconstriction and shivering thresholds, and thus increase the inter-threshold range. On the other hand, fever is a regulated increase in the thermoregulatory thresholds, but does not decrease the precision of thermoregulatory control. Taken together, the most likely prediction is that the two effects occur simultaneously; that is, the combination of general anaesthesia and fever simply produces an expanded inter-threshold range around the elevated setpoint. Then, the decrease in thermoregulatory thresholds of cold defences will diminish fever in the cold environment of around 22 °C.

Figure 4. Thermoregulation during fever and anaesthesia. The inter-threshold ranges (as defined by the difference between the sweating and vasoconstriction thresholds) were comparable on the control and the fever alone day: 0.5 ± 0.5 versus 0.4 ± 0.4 °C. In contrast, anaesthesia (Anesth) significantly increased the inter-threshold range to 1.9 ± 0.6 °C. When desflurane and IL2 were combined, the inter-threshold range was 1.2 ± 0.6 °C, which was significantly greater than during fever alone—but also significantly less than during anaesthesia alone. Reproduced from Lehhardt R et al (1999, Anesthesiology 90: 1587–1595) with permission.
which is a typical temperature in operating rooms. However, the specific effect of each intravenous anaesthetic remains to be determined.

### Practice points

- volatile anaesthesia suppresses fever in dose-dependent manner. The inhibitory mechanism appears to be mainly a central action, which decreases cold response thresholds; however, its peripheral effects on endogenous pyrogens may affect fever in some parts.
- considering that most anaesthetics and sedatives have similar thermoregulatory effects at a normal setpoint, intravenous anaesthesia might suppress fever as well as volatile anaesthesia

### Research agenda

- the effect of intravenous anaesthesia on fever needs to be evaluated.
- anaesthetic effects on endogenous pyrogens and antipyretics should be assessed to help determine the thermoregulatory effects of anaesthetics on fever.

### OPIOIDS AND FEVER

Opioids are common anaesthetic adjuvants and remain the dominant treatment for post-operative surgical pain. It is well established that opioid administration increases warm-response thresholds and decreases cold-response thresholds, thus significantly increasing the inter-threshold range. This pattern of inhibition is similar to that produced by general anaesthesia, although the magnitude is somewhat less.

Opioids also suppress fever in a dose-dependent fashion. Fentanyl and alfentanil, both μ-receptor agonists with a rapid onset, were evaluated for their effect on fever. Fentanyl, at a plasma concentration of 2.5 ng/ml, significantly reduced febrile response to IL-2 administration. Alfentanil also significantly reduced IL-2-induced fever; the reduction was comparable at high and low plasma concentrations (100 and 200 ng/ml). This may suggest that even low doses of alfentanil inhibit fever. Physicians thus need to be aware of opioid use in intensive care units or during the post-operative period because opioids can attenuate fever, which is an important symptom of infection.

The effects of fentanyl and alfentanil on plasma concentrations of cytokines were also measured in the same studies. Neither fentanyl nor alfentanil infusion shows significant effects on the plasma concentrations of cytokines induced by IL-2 administration (IL-6, IL-8, IL-10 and TNF-alpha). The interaction between opioids and immune responses has, however, been widely reported. Opioids, even at clinical doses, are immunosuppressive. Beilin et al reported that even a small dose of fentanyl suppressed natural killer cell cytotoxicity, and with a large dose the effect was long lasting. They suggest that large-dose fentanyl be used with caution, especially in cancer patients. The mechanism of the immunomodulator effect of opioids appears to be both centrally and peripherally mediated. However, the clinical relevance of
the immunomodulator effect of opioids, including its dose, tolerance, and acute and chronic administration, remains controversial.

**Practice points**
- Systemic administration of opioids seems to inhibit fever. This may require more attention to be paid to opioid use during post-operative periods or in the ICU, because fever is an important symptom of infection.

**Research agenda**
- Further evaluation of peripheral and central action of opioids on inflammatory response can help elucidate the thermoregulatory effects of opioids on fever.

**NEURAXIAL ANAESTHESIA AND FEVER**

**Thermal perturbation of neuraxial anaesthesia**

During surgery, hypothermia associated with neuraxial anaesthesia is commonly observed, although it is not as widely recognized as hypothermia during general anaesthesia. As with general anaesthesia, re-distribution is a major cause of core hypothermia during epidural and spinal analgesia. At the typical operation room temperature, core temperature decreases $0.8 \pm 0.3 \, ^\circ C$ in the first hour of epidural or spinal anaesthesia and re-distribution contributes 89% of this initial decrease. This decrease in core temperature is about half as much as occurs during general anaesthesia, and the rate is determined by the inequality between heat loss and heat production as well as block level.

Neuraxial anaesthesia also inhibits thermal control of the body by a central mechanism but to a lesser degree than general anaesthesia. However, with neuraxial anaesthesia peripheral nerve block is a more important cause of hypothermia. Sufficient core hypothermia will trigger vasoconstriction and shivering even during neuraxial anaesthesia, but only in the unblocked areas. Vasoconstriction and shivering in this limited area are usually insufficient to prevent further hypothermia. This inability of thermoregulatory defences during neuraxial analgesia sometimes induces serious hypothermia, especially during major operations requiring a high block level.

**Epidural analgesia and fever**

In spite of the thermal perturbations of neuraxial anaesthesia, epidural analgesia is frequently associated with hyperthermia, especially during labour and the post-operative period. Several studies demonstrate that average temperature is higher in patients given epidural analgesia for labour or post-operative pain treatment. The clinical importance of this paradoxical hyperthermia associated with epidural anaesthesia is that hyperthermia often prompts clinical interventions such as work-ups for infection and newborn sepsis.
It is unclear whether this core temperature elevation is true fever or passive hyperthermia. Epidural analgesia per se is unlikely to induce immunoactivation or fever. Epidural anaesthesia also reduces sweating in the blocked area. Thus, epidural analgesia can induce passive hyperthermia if metabolic expenditure increases and heat production exceeds heat loss. Therefore, epidural analgesia itself is assumed to cause hyperthermia associated with epidural analgesia, especially during labour. However, the same theory does not explain hyperthermia associated with epidural analgesia during the post-operative period. These patients have normal metabolic rates, and a hospital environment is not warm enough to induce passive hyperthermia. Patients who are not given epidural analgesia during labour or post-operative period usually receive opioids instead. Opioids such as fentanyl and alfentanil reduce the febrile response. For example, 0.2% ropivacaine epidural analgesia (with and without fentanyl) does not affect fever, whereas intravenous fentanyl infusion attenuated it (Figure 5). Such results lead to an alternative potential aetiology: hyperthermia observed in patients given epidural analgesia during labour or the post-operative period results from pyrogen-induced fever. Thus, fever is observed in patients given epidural analgesia, but not in the patients given opioids, because opioids are antipyretics.

Fever can occur by both infectious and non-infectious aetiologies. Hyperthermia associated with epidural analgesia is often observed in the patients without infection. Supporting this hypothesis, the maternal serum IL-6 concentration increases during

![Figure 5](image-url)
labour are not always associated with intra-amniotic inflammation, and IL-6 concentrations are strongly associated with intrapartum fever. It is also well known that inflammatory cytokines are increased during the post-operative period.

---

### Practice points
- epidural analgesia does not suppress fever
- it remains controversial whether epidural analgesia per se causes hyperthermia during labour or post-operative period

---

### Research agenda
- a prospective and randomized clinical trial is needed to evaluate the aetiology of epidural fever during labour

---

### PARALYSIS AND FEVER

Once fever occurs, the vasoconstriction, shivering and sweating thresholds increase synchronously. Especially at the start of fever, vasoconstriction and shivering play the important role of increasing body temperature. During anaesthesia, however, muscle relaxants are often administered for intubation or paralysis during surgical procedures. Paralysis, of course, prevents shivering and the associated increase in metabolic heat production, leaving the development of fever entirely dependent on thermoregulatory vasoconstriction. The alteration of vasomotor tone by general anaesthesia is one of the primary factors that influences intraoperative core temperature. However, it seems to be effective enough to increase core temperature during fever combined with general anaesthesia and paralysis. For example, under complete paralysis, which obliterates muscle activity and prevents increasing metabolic rate, thermoregulatory vasoconstriction was nonetheless able to maintain fever during 0.6 MAC isoflurane anaesthesia. Paralysis can reduce the magnitude of fever, but clinically its effect seems to be less important than anaesthetic-induced inhibition of fever.

---

### Practice point
- paralysis slightly reduces the magnitude of fever by preventing shivering, although its effect seems to be less important than anaesthetic-induced inhibition of fever

---

### POST-OPERATIVE FEVER

The inflammatory response can be induced by infectious or non-infectious aetiologies such as body injury, surgical procedure, malignant tumour, brain stroke etc. Fever is associated with the inflammatory responses and is usually observed...
during the post-operative period. Post-operative fevers seem to be induced mainly by the inflammatory reaction activated by surgery, but psychological stress also can induce fever. The anaesthetic technique used during surgery appears to have little effect on post-operative fever, but many drugs used in the post-operative period—such as opioids, sedatives and NSAIDs—possess immunomodulator effects and, therefore, may modulate post-operative fever.

The incidence of fever during the post-operative period seems high, but the reported numbers vary with type and duration of surgery, patient age, pre-existing inflammation and surgical site. It seems principally to be determined by the severity of surgical invasion, as well as the existence of post-operative infection.

Clinically, fever is considered the earliest and most easily detected sign of infection in surgical patients. For this reason, it is important to measure core body temperature in the early post-operative period. Post-operative changes in core temperature and plasma concentrations of IL-6 in the first 24 hours have been evaluated in the patient undergoing elective abdominal, non-cardiac thoracic or major abdominal surgeries. One fourth of the patients had a maximum urinary bladder temperature greater than 38.5 °C. The increase in core temperature was associated with shivering and vasoconstriction until the core temperature reached its peak, suggesting that this increase in core temperature was true fever. Leukocyte counts did not relate to the increase in core temperature; however, there was a positive relationship between the post-operative increase in core temperature and plasma IL-6 concentration. Only one patient of the febrile patients had an infection. This study suggests that fever during the post-operative period is common and that it may be a normal inflammatory response induced by surgical stress, not by infection. Plasma IL-6 concentration seems to be a good predictor of post-operative fever and acts as a pyrogen in post-surgical patients (Figure 6).

The fever in the post-operative period sometimes prompts diagnostic tests to determine the source or to exclude a serious infection. It is well known that work-ups for infections add extra medical costs. Because it is known that most febrile patients are bacteriologically negative routine evaluation of post-operative fever may not always be needed. Instead, clinicians should consider how common fever is in post-operative patients and restrict ‘fever work-ups’ to high-risk patients and patients in whom there are other indications of infection. Factors such as C-reactive protein (CRP) elevation, white blood cell count, and other clinical indicators should be increasingly used for the diagnosis of post-operative infection.

**Practice points**

- Fever during the post-operative period is common and may be a normal inflammatory response induced by surgical stress, not by infection.
- Physicians should restrict ‘fever work-ups’ to high-risk patients and patients with other indications of infection.
- Plasma IL-6 concentration seems to be a good predictor of post-operative fever and acts as a pyrogen in post-surgical patients.
Infection, trauma, injury and surgical stimulation all induce the inflammatory response, which includes fever. Fever is the most common problem in hospitalized patients. Although scientific knowledge about the inflammatory response is increasing, it remains controversial whether fever is beneficial or harmful to the host defence. However, there are many animal experiments and clinical observations suggesting that fever might be beneficial to the host defence.

Research agenda
- The aetiology of post-operative fever and its role should be established to allow efficient treatment of fever during the post-operative period.

**TREATMENT OF FEVER**

Fever during anaesthesia
Antipyretic therapy potentially increases the duration and severity of certain infections. Fever seems to be an adaptive response that evolved to aid the host defensive inflammatory response against pathogens. The elevated temperature enhances the activity of immune effector cells, and inhibits bacterial growth of some pathogens. This is why, historically, malarial fever and hot bath has been used for treatment of bacterial infections.

Currently, most febrile patients are treated with antipyretic, mainly for patient comfort. However, if fever renders host defences more active, it should not be treated quickly. Furthermore, fever is considered an important marker for evaluating the effectiveness of treatment. Whether fever is beneficial or harmful depends on the actual clinical circumstances, and antipyretic treatment should be evaluated on an individual basis. Letting fever take its natural course does not seem to be harmful for febrile patients. However, accompanying symptoms such as tachycardia, increased oxygen consumption, and discomfort are maladaptive for some patients, and in these cases antipyretic use ought to be considered. Specifically, fever should be treated in patients with cardiopulmonary dysfunction, acute brain stroke or injury, or in those whose temperature exceeds 40 °C.

The primary treatments for fever are amelioration of the underlying cause and administration of antipyretic medications. External active cooling including tepid sponge baths for children is not recommended for non-sedated febrile patients although it is effective for heat stroke patients with a normal thermoregulatory set point. Active cooling does not reduce core temperature, but increases the metabolic rate, activates the autonomic nervous system, and provokes thermal discomfort, because lowered skin temperature activates thermoregulatory efforts to increase the body temperature to the set point. In contrast, cutaneous cooling reduces core temperature in critical care patients who are sedated or paralysed.

Fever occurs in almost half of the patients with acute brain stroke or injury. The mechanism of this hyperthermia remains unknown, but it is known that even mild brain hyperthermia worsens the functional outcome by enhancing neurotransmitter release, exaggerating oxygen radical production, extending blood-brain barrier breakdown, and other mechanisms. In contrast, mild hypothermia seems to have neuroprotective effects on severe brain insults, and mild hypothermia (33 °C) significantly improves neurological outcomes. Thus, it is recommended that fever be combated assiduously in patients with acute brain stroke and injury to induce normothermia or mild hypothermia. Antipyretics sometimes fail to decrease core temperature in these patients; thus, external cooling combined with sedation may be the most effective method. In each case, if fever is treated, particular attention for infection will be needed because fever, a sign of infection, is diminished and mild hypothermia increases the risk of infection.

**Practice points**

- Fever may be beneficial to host defence mechanism, and should not be treated routinely.
- Fever should be treated in patients with cardiopulmonary dysfunction, acute brain stroke or injury, or in whom temperature exceeds 40 °C.
- Active cooling is not effective to reduce core temperature if the febrile patient is awake. It only increases the metabolic rate, activates the autonomic nervous system, and provokes thermal discomfort.
- Active cooling is effective for sedated and paralysed patients. It may be a useful treatment of fever in patients with acute brain stroke or injury.
Fever occurs when pyrogenic stimulation activates hypothalamic control centres. It is defined as an increase in a setpoint and there is a synchronous elevation in the cold-response and warm-response thresholds. Fever is considered to be part of acute inflammatory response; it is mediated by neuronal and hormonal factors.

During the perioperative period, fever is also modulated by exogenous factors. Volatile anaesthesia and opioids both inhibit fever. The inhibitory mechanism seems to be mainly a central action that decreases cold-response thresholds. However, other inhibitory mechanisms, such as peripheral inhibition of endogenous pyrogens, may also exist. Intravenous anaesthetics also have similar effects on thermoregulation. Therefore, it may also suppress fever in a dose-dependent manner; however, a confirming study has yet to be done. Paralysis slightly reduces the magnitude of fever by preventing shivering, although its effect seems to be less important than anaesthetic-induced inhibition of fever.

Unlike general anaesthesia, epidural analgesia does not seem to suppress fever. This may explain why fever is frequently observed in patients given epidural analgesia during labour or post-operatively.

Fever is associated with the inflammatory responses and is commonly observed post-operatively. It is usually caused by non-infectious aetiologies and most patients are bacteriologically negative. Thus, routine evaluation of post-operative fever may not always be needed. Restricting 'fever work-ups' to high-risk patients and patients with other clinical signs of infection may be recommended.

Fever should not always be treated quickly because it is probably beneficial to host defence. However, antipyretic use should be considered when accompanying symptoms, such as tachycardia or increased oxygen consumption, are harmful for the patients. Cutaneous active cooling is not effective for reducing core temperature—it increases the metabolic rate and thermal discomfort in the awake febrile patient.

**ACKNOWLEDGEMENTS**

The authors thank Daniel I. Sessler MD. (Associate Dean, Weakley Distinguished Research Chair, Director, Outcomes Research™ Institute, University of Louisville) for his support in performing the series of our fever studies and helpful comments on this manuscript.

---

**Research agenda**

- further research is warranted to better understand the fever mechanism frequently observed in patients with brain stroke and injury
- treatment strategy needs to be established for fever induced by acute stroke or brain injury

---

**SUMMARY**

Fever occurs when pyrogenic stimulation activates hypothalamic control centres. It is defined as an increase in a setpoint and there is a synchronous elevation in the cold-response and warm-response thresholds. Fever is considered to be part of acute inflammatory response; it is mediated by neuronal and hormonal factors.

During the perioperative period, fever is also modulated by exogenous factors. Volatile anaesthesia and opioids both inhibit fever. The inhibitory mechanism seems to be mainly a central action that decreases cold-response thresholds. However, other inhibitory mechanisms, such as peripheral inhibition of endogenous pyrogens, may also exist. Intravenous anaesthetics also have similar effects on thermoregulation. Therefore, it may also suppress fever in a dose-dependent manner; however, a confirming study has yet to be done. Paralysis slightly reduces the magnitude of fever by preventing shivering, although its effect seems to be less important than anaesthetic-induced inhibition of fever.

Unlike general anaesthesia, epidural analgesia does not seem to suppress fever. This may explain why fever is frequently observed in patients given epidural analgesia during labour or post-operatively.

Fever is associated with the inflammatory responses and is commonly observed post-operatively. It is usually caused by non-infectious aetiologies and most patients are bacteriologically negative. Thus, routine evaluation of post-operative fever may not always be needed. Restricting 'fever work-ups' to high-risk patients and patients with other clinical signs of infection may be recommended.

Fever should not always be treated quickly because it is probably beneficial to host defence. However, antipyretic use should be considered when accompanying symptoms, such as tachycardia or increased oxygen consumption, are harmful for the patients. Cutaneous active cooling is not effective for reducing core temperature—it increases the metabolic rate and thermal discomfort in the awake febrile patient.
REFERENCES


