EDITORIAL VIEWS

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Human Thermoregulatory Inhibition by Regional Anesthesia

Homeotherms seek to maintain a nearly constant central temperature in the face of a wide range of environmental temperatures and conditions. Afferent temperature information is received from skin,[1] muscle (possibly; see below), deep thoracic and abdominal structures,[2] the spinal cord[3] and the brain.[4] This information is integrated in the central nervous system at various sites ascending from the spinal cord to the hypothalamus.[5] In the simplest model of thermoregulatory control, responses are either turned on or off in response to variations in hypothalamic temperature around a "set point."[6] In a second model, the integrated afferent signal is compared with thresholds for various autonomic thermoregulatory mechanisms. If the integrated signal exceeds the thresholds for temperature dissipating mechanisms (*i.e.*, active vasodilation and sweating), or decreases to less than the thresholds for temperature conserving or heat producing mechanisms (vasoconstriction, nonshivering thermogenesis and shivering), efferent discharge initiates activity in appropriate effector organs.

The range in core temperature between various thermoregulatory mechanisms has been referred to either as the dead zone[7] or null zone[8] (zone between sweating and shivering thresholds), and more recently the interthreshold range (range between sweating and vasoconstriction thresholds).[9] Within this interthreshold range (which is ~ 0.2°C under normal conditions), core temperature varies passively without active thermoregulation. Each thermoregulatory response increases in intensity as the difference between the integrated thermal signal and the given response threshold increases. The increase in activity *versus* change in signal is referred to as the proportionality constant or response gain.

The integrity and effectiveness of the thermoregulatory system is adversely affected by several factors including age,[10] disease,[11] injury,[12] ethanol,[13] and various pharmacologic agents.[14] Specifically, anesthetics have been shown to inhibit thermoregulatory control in animals[15] and humans.[16] As a result, anesthetized patients often become hypothermic during surgery. After induction of anesthesia, peripheral vasodilation subsequent to thermoregulatory inhibition allows redistribution of heat from the core thermal compartment to cooler peripheral tissues.[17] Normal thermoregulatory heat production is inhibited[18] and cutaneous heat loss exceeds heat production.

Perioperative hypothermia may predispose to complications including postoperative shivering (which adversely increases metabolic rate and cardiac work and may also disrupt surgical repair or result in wound dehiscence),[19] impaired coagulation,[20] decreased cutaneous blood flow,[21] slowed drug metabolism,[22] and decreased resistance to surgical wound infection.[23] It is therefore appropriate to either prevent the onset of hypothermia or at least minimize possible complications by rapidly restoring normal core temperature. Consequently a thorough understanding of human thermoregulation, the effects of anesthetics on the control systems, and the mechanisms for these observed effects, will assist the clinician in perioperative thermal management.

This issue of ANESTHESIOLOGY contains two reports that further our understanding of perianesthetic thermoregulation.[24,25] In the past, these authors[9] and others[7,8] convincingly documented a distinct interthreshold range (in contrast to a single "set point") and demonstrated that inhaled or intravenous anesthetic agents[16,26–31] widen the interthreshold range without affecting the gains or maximum intensities of thermoregulatory responses. Similar effects of epidural[32,33] and spinal[34] anesthesia have also been recently reported. In one of these papers in this issue of ANESTHESIOLOGY, Ozaki *et al.*[24] compared thermoregulatory thresholds for sweating, vasoconstriction and shivering in volunteers given epidural anesthesia, spinal anesthesia, and no anesthesia. They also compared the shivering thresholds in two groups of surgical patients given either epidural or spinal anesthetic. The authors state that epidural anesthesia primarily involves blockade of the spinal nerve roots, whereas spinal anesthesia acts

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directly on the spinal cord. Because the spinal cord not only integrates afferent information but also provides afferent input to higher thermoregulatory centers, the authors propose that spinal and epidural anesthesia may influence thermoregulatory processing differently.

Regional anesthesia had no effect on the vasoconstriction threshold but slightly increased the sweating threshold and slightly decreased the shivering threshold compared with thresholds in the nonanesthetized condition. The significant increases in sweating-to-vasoconstriction and vasoconstriction-to-shivering interthreshold ranges were similar with epidural and spinal anesthesia. Ozaki *et al.*[24] conclude that thermoregulatory impairment during regional anesthesia is due to blockade of afferent peripheral temperature information (this mechanism is addressed below). The authors also postulate that all response thresholds would be reduced by regional anesthesia if warm and cold afferent information were processed as integrated information. They therefore propose the divergence of the sweating and shivering thresholds as evidence that is most consistent with independent thermoregulatory processing of warm and cold afferent signals. Satinoff[35] provided a framework for such a thermoregulatory model, with separate controllers for various effector responses.

Sessler and coworkers[9,24,25] have developed a protocol for separately controlling skin and core temperatures. Cutaneous temperature is controlled by a combination of external heat exchangers (forced-air warming cover and circulating water blanket). Core temperature is then independently decreased by central venous infusion of cold lactated Ringers solution (~4°C) through a catheter previously introduced into the superior vena cava *via* the right internal jugular vein. Although independent temperature control has been achieved with internal heat exchangers in animals[36,37] and core temperature increased by heating nonsentient areas of a paraplegic man,[7] the current protocol has not been performed in normal humans by other groups. This protocol itself is a significant contribution to the field of thermoregulatory control.

This study[24] is the first to compare the thermoregulatory consequences of epidural and spinal anesthesia with a control (nonanesthetized) condition in which temperature of sentient skin (upper body) is controlled at the same values. The use of volunteers in a repeated-measures design in these tightly controlled studies allows confident conclusions about the comparable thermoregulatory effects of regional anesthesia.

The basic nature of this study may present some methodologic problems. Although surgical patients usually cool during surgery and rewarm during recovery, the volunteers were first warmed and then cooled. Under the latter conditions there may be some degree of hysteresis in heat dissipating responses. It is important to note however, that shivering thresholds were also virtually identical in the patients given epidural and spinal anesthesia under normal clinical conditions. As well, sentient skin temperature was higher (36°C) than would normally be experienced by cool surgical patients (30–33°C). Both shortcomings are necessary limitations of the protocol. Core temperature was initially increased toward the sweating threshold by upper body warming. Once this threshold was reached it was necessary to maintain skin temperature to determine the isolated effect of changing (decreasing) core temperature. This higher cutaneous temperature is proposed as the reason why the shivering threshold in the volunteers is 1°C lower than in the surgical patients. It may also explain the smaller interthreshold ranges seen in this study[24] compared with those in the study by Emerick *et al.*[25] and other studies.[34,38] Despite the above limitations, this is the best human model available to date, and qualitative errors are unlikely.

Further considerations include the possible diffusion, absorption and recirculation of the anesthetic agents. It is unlikely that epidural or spinal injectant diffuses rostrally to the brain in concentrations high enough to impair central thermoregulation. Alternatively, epidural anesthetic might exert an indirect effect if the local anesthetic was absorbed into the blood stream and transported to the central nervous system. Although the authors minimize this likelihood because of the rapid metabolism of 2-chloroprocaine (the epidural agent used in this study), this effect cannot be ruled out without further study.

One final confounding factor is that epidurally administered local anesthetic diffuses into the subarachnoid space. In fact, epidural procaine has been detected in spinal fluid at the threshold concentration for spinal anesthesia.[39] In the current study, similar diffusion of 2-chloroprocaine, if it occurred, may confound the attempt to differentiate between the effects of blocking spinal nerve roots and those of blocking the spinal cord itself. In any case the practical finding, that both methods of regional anesthesia impair thermoregulation to the same extent, would still be accurate and clinically important.

There are many studies describing thermoregulatory dysfunction during anesthesia, however, little is known about the actual mechanisms for these effects. As discussed earlier, it is unlikely that regional anesthesia impairs centrally mediated thermoregulation either by diffusion of local anesthetics along the spinal cord or systemic absorption of the anesthetic in the blood. In the other paper from these investigators, by Emerick *et al.*,[25] also published in this issue of ANESTHESIOLOGY, a specific mechanism for the effect of regional anesthesia on thermoregulation was tested. Conduction anesthesia blocks all thermal sensations, however, cold signals are disproportionately affected because cold receptor activity is predominant at typical skin temperatures. The authors postulated that regional anesthesia would cause thermoregulatory control centers to detect a higher temperature in the legs. This higher *apparent* leg temperature would consequently decrease the core temperature threshold for shivering.

Volunteers were studied in three nonanesthetized conditions, in which the leg-skin temperature was cold (~32°C), warm (~36°C), or hot (~38°C), and once during epidural anesthesia without leg-warming. Upper body skin temperature was maintained at the same temperature (~35.7°C) for all four trials and core temperature was decreased by the technique of central venous infusion of cold lactated Ringers solution (3°C). Leg-tissue temperature also was estimated by a previously described technique.[40,41] The apparent temperature was inferred from the actual leg temperature required to induce a reduction in the shivering threshold comparable to that observed during epidural anesthesia. The relative contribution of leg temperature to the total thermal afferent input was also calculated. Apparent skin and apparent tissue temperatures were significantly greater than actual leg-skin and leg-tissue temperatures at the shivering threshold by 4.1 and 2.3°C respectively. The calculated contribution of leg-skin temperature and leg-tissue temperature to the shivering threshold was 11% and 19% of the core contribution respectively. The apparent contribution of muscle temperature sensors is of considerable interest and merits further study.

This work by Emerick *et al.*[25] differs from previous studies in humans, which primarily have been phenomenologic. Working with a fully integrated thermoregulatory system in a normal human volunteer provides the advantage that intact responses can be studied. However, a disadvantage occurs when faced with the more basic task of describing specific mechanisms. There are limitations in the manipulations and interventions that are acceptable in a human model. Despite these constraints, the authors provide the first evidence supporting a specific mechanism by which the peripheral effects of regional anesthesia impair centrally mediated thermoregulatory control. These difficult studies were well controlled, and measurements accurately taken. The authors' ability to identify precise linear regressions in individual volunteers, over a range of core temperatures less than 1°C on the three different days, indicates the remarkable precision of the thermoregulatory control system.

Although the hypothesis in this study is not immediately intuitive, it is logical in retrospect. Patients undergoing regional anesthesia report a sensation of warmer leg-skin temperature after complete block occurs.[42] It is certainly plausible that if an increase in leg temperature is perceived at a conscious level, an apparent increase could also be sensed at thermoregulatory control centers. After induction of regional anesthesia, the impairment of thermoregulatory vasoconstriction results in an actual increase in leg-skin temperature of about 1°C. This actual increase however, is not sensed because afferent conduction from warm thermal sensors is blocked. As the authors point out, simultaneous blocking of predominantly cold input would produce the same effect, namely to increase the temperature sensed by central thermoregulatory centers. This elegant study provides evidence for just such an increase. Although the data support the hypothesis quite convincingly, this study does not eliminate all other potential mechanisms for the observed thermoregulatory deficit. It often is dangerous to insist on the existence of a single operational mechanism (and the authors do not do so), and further work confirming the current mechanism and addressing others is warranted.

In tandem, these two publications provide valuable insights into human thermoregulation during regional anesthesia. This research has important clinical implications. This and other work[43] indicate that hypothermia is common during epidural and spinal anesthesia and may be nearly as severe as during general anesthesia. In light of the many complications of mild hypothermia, temperature monitoring and thermal management should be considered with these forms of regional anesthesia. Equally important from the viewpoint of basic science is that this work should stimulate investigation in areas including determination of whether peripheral cold and warm afferent signals

are processed separately or as an integrated signal, as well as confirmation, description, and quantification of the effects of putative muscle thermal receptors. Much work can still be done to separate core and peripheral thermal inputs further and more specifically to determine the relative contributions of different skin surface areas or tissues to the total input for various thermoregulatory responses.

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