

The Thermoregulation Story

Daniel I. Sessler, M.D.*

The Thermoregulatory Threshold in Humans during Halothane Anesthesia. By Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ. *ANESTHESIOLOGY* 1988; 68:836–42. Reprinted with permission.

Abstract: Although suppression of thermoregulatory mechanisms by anesthetics is generally assumed, the extent to which thermoregulation is active during general anesthesia is not known. The only thermoregulatory responses available to anesthetized, hypothermic patients are vasoconstriction and nonshivering thermogenesis. To test anesthetic effects on thermoregulation, the authors measured skin-surface temperature gradients (forearm temperature – fingertip temperature) as an index of cutaneous vasoconstriction in unpremedicated patients anesthetized with 1% halothane and paralyzed with vecuronium during elective, donor nephrectomy. Patients were randomly assigned to undergo maximal warming (warm room, humidified respiratory gases, and warm intravenous fluids; $n = 5$) or standard

temperature management (no special warming measures; $n = 5$). Skin-surface temperature gradients of 4°C or more were prospectively defined as significant vasoconstriction. Normothermic patients (average minimum esophageal temperature = $36.4^{\circ} \pm 0.3^{\circ}\text{C}$ [SD]) did not demonstrate significant vasoconstriction. However, each hypothermic patient displayed significant vasoconstriction at esophageal temperatures ranging from 34.0 to 34.8°C (average temperature = $34.4^{\circ} \pm 0.2^{\circ}\text{C}$). These data indicate that active thermoregulation occurs during halothane anesthesia, but that it does not occur until core temperature is approximately 2.5°C lower than normal. In two additional hypothermic patients, increased skin-temperature gradients correlated with decreased perfusion as measured by a laser Doppler technique. Measuring skin-surface temperature gradients is a simple, noninvasive, and quantitative method of determining the thermoregulatory threshold during anesthesia.

WHILE an anesthesia resident at the University of California, Los Angeles—approximately 30 yr ago—I started thermoregulatory research under the guidance of the anesthesiologist and physiologist Eduardo Rubinstein, M.D., Ph.D. (Professor Emeritus of Anesthesiology). At that

* Michael Cudahy Professor and Chair, Department of OUTCOMES RESEARCH, Cleveland Clinic, Cleveland, Ohio.

Received from the Department of OUTCOMES RESEARCH, Cleveland Clinic, Cleveland, Ohio. Submitted for publication September 12, 2012. Accepted for publication October 1, 2012. Supported by institutional and/or departmental sources. The Department of OUTCOMES RESEARCH is supported by the National Institutes of Health, Bethesda, Maryland, the Canadian Institutes of Health Sciences, Ottawa, Ontario, Canada, and numerous companies. Dr. Sessler serves on an Advisory Board for 3M, St. Paul, Minnesota, and donates all fees to charity. He has no personal financial interest related to this article.

Address correspondence to Dr. Sessler: Department of OUTCOMES RESEARCH, Cleveland Clinic, 9500 Euclid Ave — P77, Cleveland, Ohio 44195. ds@or.org. On the world wide web: www.or.org. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Copyright © 2012, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. *ANESTHESIOLOGY* 2013; 118:181–6



time hypothermia was considered a normal consequence of surgery, and not thought to be especially harmful. Few

patients were warmed with anything other than relatively ineffective circulating-water mattresses; postoperative core temperatures after major abdominal surgery (all open in those days) was typically approximately 34.5°C.

Naturally, I started with a literature search. There were only approximately 30 articles about temperature in anesthesia at the time, including some about the problem of *hyperthermia* in unconditioned tropical operating rooms; approximately half were review articles—mostly by the same person. They all presented the same simple perspective: (1) anesthesia obliterates thermoregulatory defenses, making patients poikilothermic; (2) patients get cold during surgery because of excessive heat loss; and (3) postoperative reemergence of thermoregulatory control triggers shivering (“up to 400% increase in metabolic rate”!), which is the only serious complication of mild perioperative hypothermia. None of these conclusions were based on data.

Because I was a resident and did not have dedicated research time, I needed a project that was technically easy and could be done in the course of my routine clinical work. Eduardo told me to “go measure temperature; it’s easy.” Temperature monitoring is of course technically easy; but it turned out that the physiology of perioperative thermoregulation and heat balance was anything but simple.

We started our measurements in the recovery room (the term “post-anesthesia care unit” had yet to be invented). In those days, the American Board of Anesthesiology was less proscriptive about rotations, and the recovery room was hardly popular; I was thus able to spend 4 or 5 months collecting postoperative temperature and shivering data. The results were not encouraging: shivering was common enough, but inconsistently related to core temperature or thermoregulatory vasoconstriction. We finally concluded that the physiology described in review articles of the period was simply wrong. Roughly speaking, I spent the next 15 yr disproving nearly every concept and conclusion presented in these reviews.

Upon completion of my residency, the University of California at San Francisco hired me because they needed a pediatrician-anesthesiologist with a chemistry background to help start a magnetic resonance spectroscopy project. In fact, my chemistry background was trivial; I was a chemistry major at the University of California, Berkeley, but left for the Columbia University College of Physicians and Surgeons, New York, New York, after 3 yr. I think Ronald Miller, M.D. (Professor, Department of Anesthesia, University of California, San Francisco) confused me with my brother, Jonathan L. Sessler, Ph.D., who is a well-known chemist with whom I have since collaborated.¹

I spent my first year in San Francisco doing magnetic resonance spectroscopy, but then returned to clinical thermoregulation. Some members of the department made no secret of the fact that they thought I was abandoning “real science.” However, George Gregory, M.D. (Professor, Department of Anesthesia, University of California, San Francisco) was

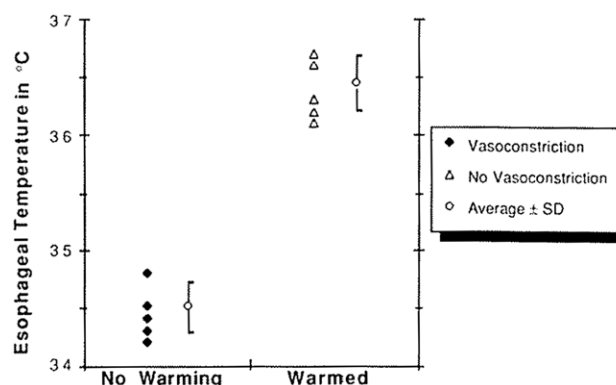


Fig. 1. Significant vasoconstriction was observed in five patients who became hypothermic during open donor nephrectomy (left side of figure). Vasoconstriction did not occur in five other patients who were kept normothermic (right side of figure). Thermoregulatory vasoconstriction was prospectively defined as a skin-surface temperature gradient (forearm temperature – fingertip temperature) of 4°C or more. The thermoregulatory threshold (triggering core temperature) with halothane 0.86% in oxygen was $34.4^{\circ} \pm 0.2^{\circ}\text{C}$ (SD). Reproduced with permission from Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ: The thermoregulatory threshold in humans during halothane anesthesia. *ANESTHESIOLOGY* 1988; 68: 836–42.

encouraging, as was Henry Rosenberg, M.D. (Professor and Director of Medical Education, Department of Anesthesia, St. Barnabas Medical Center, Livingston, New Jersey) then at Hahnemann Hospital, Philadelphia, Pennsylvania. Professor Edmond Eger II, M.D., and Professor Emeritus John Severinghaus, M.D. (both from the Department of Anesthesia, University of California, San Francisco), from among others, were generous with their advice and mentorship.

It would be dishonest to say that I had any idea at the time how the thermoregulation story would play out. In fact, at one point, I made a conscious decision to study thermoregulatory reflexes because they interested me *even though I did not believe them to be clinically important*. It seems I was wrong...

The first, and perhaps most real, thermoregulatory study (abstract above) was published in *ANESTHESIOLOGY* in 1988² accompanied by an editorial by the great thermoregulatory physiologist Ted Hammel, Ph.D.³ There are at least five interesting aspects of this study. Perhaps most importantly, it was the first study to show that anesthetized mammals are not poikilothermic; instead, humans who are given halothane do trigger thermoregulatory vasoconstriction in response to hypothermia, but not until core temperature reaches $34.4^{\circ} \pm 0.2^{\circ}\text{C}$ (normal approximately 36.5°C). In contrast, no patients randomized to normothermia vasoconstricted, demonstrating that vasoconstriction was a specific thermoregulatory defense, rather than resulting from hypovolemia or some irrelevant cause (fig. 1).

In subsequent studies, we quantified thermoregulatory vasoconstriction with nearly every volatile and intravenous

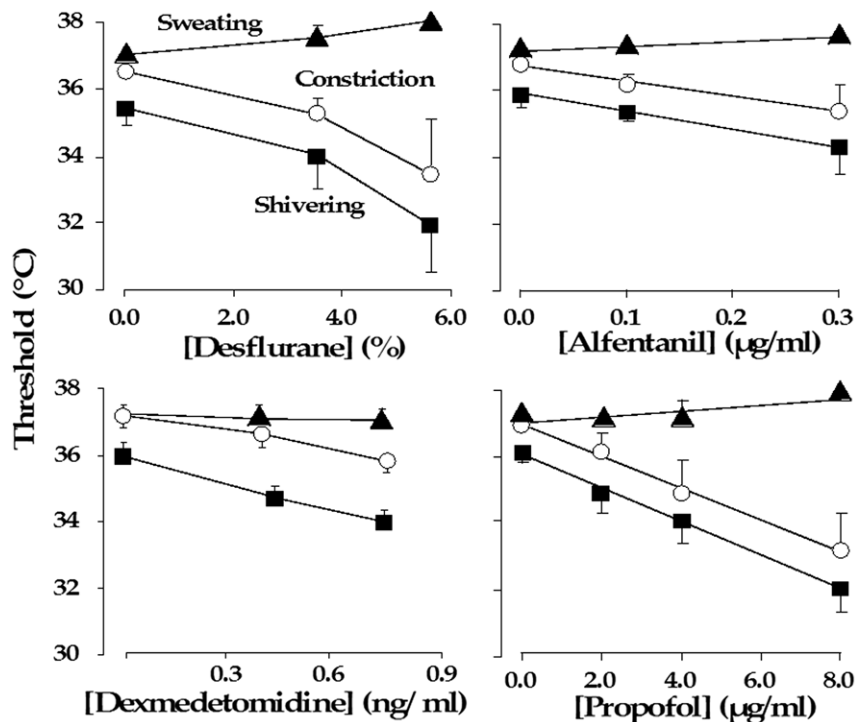


Fig. 2. The major autonomic thermoregulatory response thresholds in volunteers given desflurane, alfentanil, dexmedetomidine, or propofol. All the anesthetics slightly increase the sweating threshold (triggering core temperature), while markedly and synchronously decreasing the vasoconstriction and shivering thresholds. SD bars smaller than the data markers have been deleted. Reproduced with permission from Annadata RS, Sessler DI, Tayefeh F, Kurz A, Dechert M: Desflurane slightly increases the sweating threshold, but produces marked, nonlinear decreases in the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 83:1205–11; Kurz A, Go JC, Sessler DI, Kaer K, Larson M, Bjorksten AR: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 83:293–9; Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C: Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 87:835–841, 1997; and Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C: Propofol linearly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 82:1169–80.

anesthetic. Each drug has a unique dose–response curve, being linear for intravenous drugs,^{4–6} but having disproportionate effect at high concentrations with volatile anesthetics.^{7–10} Nonetheless, clinical doses of most drugs and drug combinations seem to trigger thermoregulatory vasoconstriction at core temperatures near 34.5°C (fig. 2).

The second interesting facet of our study was the demonstration that core temperature stabilized at the time of vasoconstriction. Thermoregulatory vasoconstriction is thus clinically important even during anesthesia, and prevents further hypothermia. How vasoconstriction constrains metabolic heat to the core thermal compartment is complicated and was subsequently quantified by Andrea Kurz *et al.*¹¹ (Kurz remains my longest-term and closest collaborator) using measurement techniques and models developed in collaboration with my physicist father, Andrew M. Sessler, Ph.D.^{12,13} But suffice it to say that vasoconstriction is remarkably effective and explains why postoperative temperatures in unwarmed patients are rarely less than 34.5°C, no matter how large or long the operation might be.

In the absence of anesthesia, the thresholds (triggering core temperatures) for vasoconstriction and sweating are within a

few tenths of a degree Celsius. In fact, the difference between these two thresholds defines normal body temperature, with small deviations in either direction triggering effective defenses. It is thus reasonable to use a “setpoint” model of thermoregulatory control in unanesthetized mammals, in which the thermoregulatory controller operates much like a home thermostat, being either fully “on” or fully “off.” But during anesthesia, the difference between these initial autonomic warm and cold defenses increases 10–20-fold depending on the type of anesthesia and its dose. A further complication is that even once triggered, each response has a gain (incremental increase per further temperature deviation)^{9,14–17} and maximum response intensity,^{14–16} which are also altered by general and neuraxial anesthetics. The third interesting aspect of our article is thus that it set the stage for a novel thermoregulatory model that accounts for individual and not-necessarily coordinated alterations in threshold, gain, and maximum response intensity. This model has become the standard for both clinical and physiologic studies.

The fourth interesting facet of our study is that it presented a novel methodology for evaluating vasoconstriction.

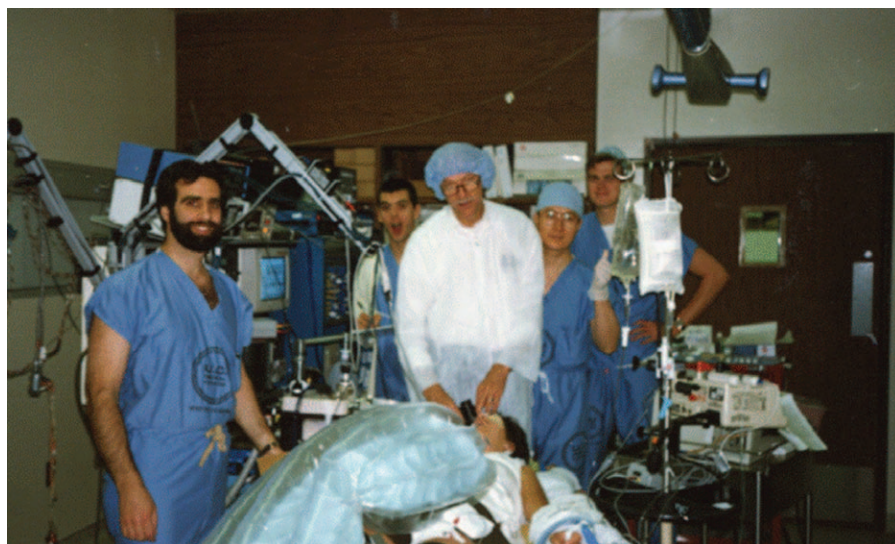


Fig. 3. Photograph of a volunteer study circa 1992. The author is at the left. Professor Merlin Larson is in white. Immediately to his right is research fellow Takehiko Ikeda, now Associate Professor at the National Defense Medical College in Japan. And to the far right is graduate student Marc Schroeder, now Chair of Anesthesia at Alta Bates Summit Medical Center in Oakland, California. He is among five of the author's students who subsequently chaired anesthesia departments.

Skin-temperature gradients, the difference between forearm and fingertip temperature, turns out to be a reliable measure of thermoregulatory vasoconstriction, which correlates extremely well with laser Doppler and the gold standard for flow, volume plethysmography.¹⁸

The basis for skin-temperature gradients is arterio-venous shunts in the fingers and toes, which are specialized

high-capacity vessels that are designed to dissipate heat rather than provide local nutrition. (A given length of shunt conveys 10,000 times as much blood as a capillary.) When the central thermoregulatory controller opens shunts, the flow is so high that finger temperature increases to nearly core temperature. In contrast, finger flow is restricted to metabolic needs when the shunts are closed. Because fingers require little oxygen, finger temperature then decrease to nearly ambient temperature. The forearm is simply a skin-surface reference temperature that compensates for changes in ambient temperature. Because gradients are technically simple and resistant to artifact, they have since been used as a measure of thermoregulatory vasoconstriction (and finger flow, more generally) in hundreds of articles.

And finally, it is worth noting that our primary results are based on just 10 patients who were randomized to hypothermia (routine care at the time) or extra warming. Furthermore, the measurements were technically simple, consisting of just core temperature and two skin-surface temperatures. The study thus took only a couple of months to complete, and cost virtually nothing. But of course it was based on several years of (mostly) failed preliminary studies. So it is possible to make important advances with small, inexpensive, and technically simple studies—although considerable effort may be necessary to get to the point of knowing what to do.

This initial article on the vasoconstriction threshold during halothane anesthesia was the first of a few-hundred temperature-related studies. It led most immediately to the evaluation of dose-dependent effects of most anesthetics on the thresholds for sweating, vasoconstriction, and shivering—along with their effects on gain and maximum response intensity. The results were generally consistent with those for halothane: all anesthetics impair thermoregulatory control, but patients consistently respond to sufficient core and skin-temperature perturbations.⁴⁻¹⁰ Many of these studies were conducted in volunteers, which permitted exquisite control of thermal conditions, and allowed us to

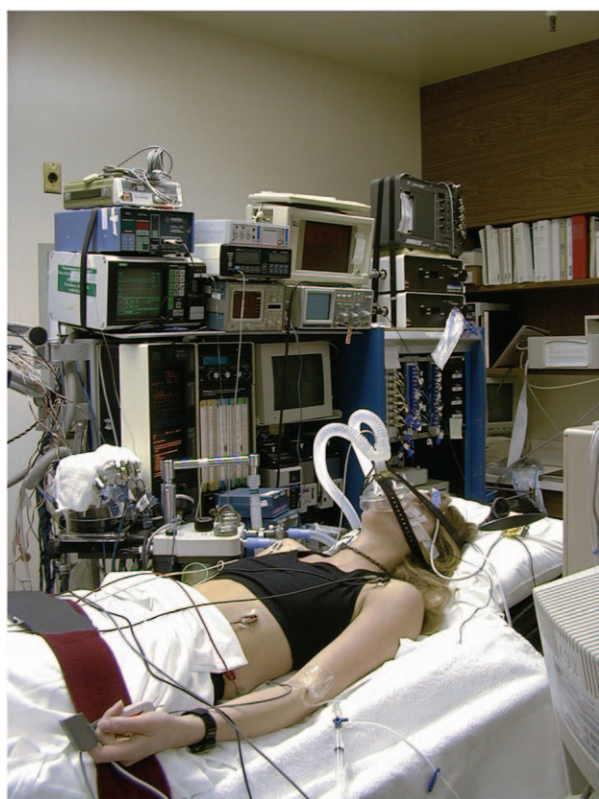


Fig. 4. A volunteer in the Human Study Laboratory at the University of California, San Francisco, circa 2002. Part of the author's home-built thermoregulatory data-acquisition system is in the background.

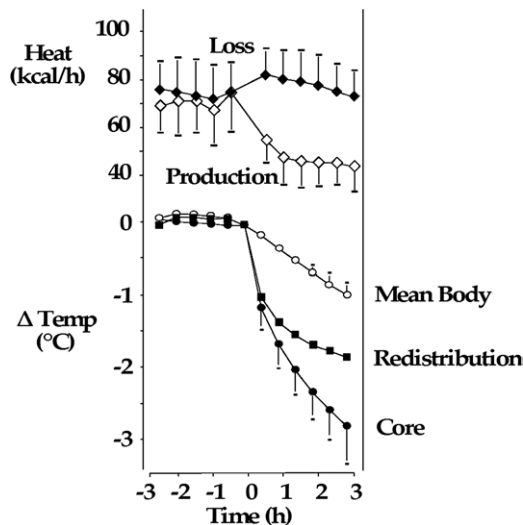


Fig. 5. Changes in body heat content and distribution of heat within the body during induction of general anesthesia (elapsed time zero). The change in mean body temperature was subtracted from the change in core (tympanic membrane) temperature, leaving the core hypothermia specifically resulting from redistribution. Redistribution hypothermia was thus not a measured value; instead, it is defined by the decrease in core temperature not explained by the relatively small decrease in systemic heat content. After 1 h of anesthesia, core temperature had decreased $1.6^{\circ} \pm 0.3^{\circ}\text{C}$, with redistribution contributing 81% to the decrease. Even after 3 h of anesthesia, redistribution contributed 65% to the entire $2.8^{\circ} \pm 0.5^{\circ}\text{C}$ decrease in core temperature. Results are presented as means \pm SD. Reprinted with permission from Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C: Heat flow and distribution during induction of general anesthesia. *ANESTHESIOLOGY* 1995; 82:662–73.

use powerful crossover study designs that produced reliable results with relatively few participants (figs. 3 and 4).

In the course of our threshold studies, we noticed that core temperature decreases precipitously during the initial hour of anesthesia, sometimes a full degree Celsius in just 30 min. The observation was not entirely new, but had always been attributed to heat loss from patients being undressed in a cool environment and to skin preparation with liquids that were allowed to evaporate. The difficulty is that to dissipate so much heat, mean skin temperature would have to increase to approximately 44°C —which clearly does not happen. That led to better understanding of thermal compartments and heat flow within the body. In fact, the initial hypothermia after induction of anesthesia is approximately 80% explained by core-to-peripheral redistribution of body heat rather than heat loss to the environment (fig. 5).^{12,19} Subsequent studies demonstrated that internal flow of heat is a major determinant of core temperature under a wide variety of circumstances and is arguably as important as environmental heat balance.^{11,20,21} A clinical consequence

is that redistribution hypothermia can be largely prevented by prewarming patients before induction of anesthesia.^{22–24}

A decade after starting to study thermoregulation, there was scant evidence that mild perioperative hypothermia caused any complications more serious than shivering and thermal discomfort. But there were increasingly compelling reasons to believe that it might. We thus conducted randomized trials evaluating the effects of hypothermia on surgical wound infections and coagulopathy, finding that each complication was markedly enhanced by just $1^{\circ}\text{--}2^{\circ}\text{C}$ of hypothermia.^{25,26} A year later, in 1997, Frank *et al.*²⁷ published the results of a trial showing that mild hypothermia causes morbid cardiac outcomes. Other studies followed in which we showed that mild hypothermia decreases drug metabolism^{28,29} and prolongs recovery.³⁰ There are now more than 25 randomized trials demonstrating the adverse effects of mild perioperative hypothermia.

The clear causal link between hypothermia and serious outcomes involving numerous systems made the maintenance of normothermia a new standard-of-care. Maintaining normothermia is, in fact, now a “pay-for-performance” measure and routine in the United States. The need to maintain normothermia in turn led to dozens of studies evaluating heat transfer under various conditions and with various devices—work that continues. Other areas of interest included neuraxial anesthesia,^{31–33} fever,^{34–37} and blunting thermoregulatory responses to facilitate induction of therapeutic hypothermia.^{38–40} Recognition that halothane impairs thermoregulatory defenses, but does not obliterate them, was thus the first step in understanding why and how surgical patients become hypothermic. That, in turn, led to an appreciation of just how harmful even mild hypothermia can be, and subsequently to good methods of preventing hypothermia.

For more than a decade after our initial thermoregulatory studies, we largely restricted our work to temperature-related investigations. However, we expanded to other topics when the Thermoregulation Group at the University of California in San Francisco became the Outcomes Research Institute at the University of Louisville, and subsequently the Department of Outcomes Research at the Cleveland Clinic. The Department of Outcomes Research—which has no clinical responsibility—has 40 full-time research personnel. The Department is the coordinating center for the international Outcomes Research Consortium,[†] the world’s largest clinical anesthesia research group. The Consortium coordinates approximately 100 studies at any given time, and publishes an average of a full paper per week—representing approximately 10% of the world’s clinical anesthesia research.⁴¹

References

1. Sessler JL, Sessler DI: Anesthesia — Don’t forget your chemistry, Letters to a Young Chemist. Edited by Ghosh A. Weinheim, Germany, Wiley-VCH, 2011
2. Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ: The thermoregulatory threshold in humans during halothane anesthesia. *ANESTHESIOLOGY* 1988; 68:836–42

[†] www.ORG. Accessed November 29, 2012.

3. Hammel HT: Anesthetics and body temperature regulation. *ANESTHESIOLOGY* 1988; 68:833–5
4. Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C: Propofol linearly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 82:1169–80
5. Kurz A, Ikeda T, Sessler DI, Larson MD, Bjorksten AR, Dechert M, Christensen R: Meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold. *ANESTHESIOLOGY* 1997; 86:1046–54
6. Kurz A, Go JC, Sessler DI, Kaer K, Larson MD, Bjorksten AR: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 83:293–9
7. Xiong J, Kurz A, Sessler DI, Plattner O, Christensen R, Dechert M, Ikeda T: Isoflurane produces marked and nonlinear decreases in the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1996; 85:240–5
8. Sessler DI, McGuire J, Hynson J, Moayeri A, Heier T: Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases cutaneous heat loss. *ANESTHESIOLOGY* 1992; 76:670–5
9. Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K: Desflurane reduces the gain of thermoregulatory arteriovenous shunt vasoconstriction in humans. *ANESTHESIOLOGY* 1995; 83:1212–9
10. Kurz A, Plattner O, Sessler DI, Huemer G, Redl G, Lackner F: The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than in young patients. *ANESTHESIOLOGY* 1993; 79:465–9
11. Kurz A, Sessler DI, Christensen R, Dechert M: Heat balance and distribution during the core-temperature plateau in anesthetized humans. *ANESTHESIOLOGY* 1995; 83:491–9
12. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C: Heat flow and distribution during induction of general anesthesia. *ANESTHESIOLOGY* 1995; 82:662–73
13. Belani K, Sessler DI, Sessler AM, Schroeder M, McGuire J, Merrifield B, Washington DE, Moayeri A: Leg heat content continues to decrease during the core temperature plateau in humans anesthetized with isoflurane. *ANESTHESIOLOGY* 1993; 78:856–63
14. Kim JS, Ikeda T, Sessler DI, Turakhia M, Jeffrey R: Epidural anesthesia reduces the gain and maximum intensity of shivering. *ANESTHESIOLOGY* 1998; 88:851–7
15. Ikeda T, Sessler DI, Tayefeh F, Negishi C, Turakhia M, Marder D, Bjorksten AR, Larson MD: Meperidine and alfentanil do not reduce the gain or maximum intensity of shivering. *ANESTHESIOLOGY* 1998; 88:858–65
16. Ikeda T, Kim JS, Sessler DI, Negishi C, Turakhia M, Jeffrey R: Isoflurane alters shivering patterns and reduces maximum shivering intensity. *ANESTHESIOLOGY* 1998; 88:866–73
17. Greif R, Laciny S, Rajek A, Doufas AG, Sessler DI: The threshold and gain of thermoregulatory vasoconstriction differs during anesthesia in the dependent and upper arms in the lateral position. *Anesth Analg* 2002; 94:1019–22
18. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. *ANESTHESIOLOGY* 1990; 73:541–5
19. Matsukawa T, Sessler DI, Christensen R, Ozaki M, Schroeder M: Heat flow and distribution during epidural anesthesia. *ANESTHESIOLOGY* 1995; 83:961–7
20. Szmuk P, Ezri T, Sessler DI, Stein A, Geva D: Spinal anesthesia speeds active postoperative rewarming. *ANESTHESIOLOGY* 1997; 87:1050–4
21. Rajek A, Greif R, Sessler DI, Baumgardner J, Laciny S, Bastanmehr H: Core cooling by central venous infusion of ice-cold (4 degrees C and 20 degrees C) fluid: Isolation of core and peripheral thermal compartments. *ANESTHESIOLOGY* 2000; 93:629–37
22. Camus Y, Delva E, Sessler DI, Lienhart A: Pre-induction skin-surface warming minimizes intraoperative core hypothermia. *J Clin Anesth* 1995; 7:384–8
23. Leslie K, Sessler DI: Perioperative hypothermia in the high-risk surgical patient. *Best Pract Res Clin Anaesthesiol* 2003; 17:485–98
24. Sessler DI, Schroeder M, Merrifield B, Matsukawa T, Cheng C: Optimal duration and temperature of prewarming. *ANESTHESIOLOGY* 1995; 82:674–81
25. Kurz A, Sessler DI, Lenhardt R: Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med* 1996; 334:1209–15
26. Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A: Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. *Lancet* 1996; 347:289–92
27. Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, Beattie C: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. *JAMA* 1997; 277:1127–34
28. Heier T, Caldwell JE, Sessler DI, Miller RD: Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *ANESTHESIOLOGY* 1991; 74:815–9
29. Leslie K, Sessler DI, Bjorksten AR, Moayeri A: Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. *Anesth Analg* 1995; 80:1007–14
30. Lenhardt R, Marker E, Goll V, Tschernich H, Kurz A, Sessler DI, Narzt E, Lackner F: Mild intraoperative hypothermia prolongs postanesthetic recovery. *ANESTHESIOLOGY* 1997; 87:1318–23
31. Ozaki M, Kurz A, Sessler DI, Lenhardt R, Schroeder M, Moayeri A, Noyes KM, Rotheneder E: Thermoregulatory thresholds during epidural and spinal anesthesia. *ANESTHESIOLOGY* 1994; 81:282–8
32. Kurz A, Sessler DI, Schroeder M, Kurz M: Thermoregulatory response thresholds during spinal anesthesia. *Anesth Analg* 1993; 77:721–6
33. Joris J, Ozaki M, Sessler DI, Hardy AF, Lamy M, McGuire J, Blanchard D, Schroeder M, Moayeri A: Epidural anesthesia impairs both central and peripheral thermoregulatory control during general anesthesia. *ANESTHESIOLOGY* 1994; 80:268–77
34. Lenhardt R, Negishi C, Sessler DI, Ozaki M, Tayefeh F, Kurz A: Paralysis only slightly reduces the febrile response to interleukin-2 during isoflurane anesthesia. *ANESTHESIOLOGY* 1998; 89:648–56
35. Lenhardt R, Negishi C, Sessler DI, Ozaki M, Ettinger K, Bastanmehr H, Lobo E: The effect of pyrogen administration on sweating and vasoconstriction thresholds during desflurane anesthesia. *ANESTHESIOLOGY* 1999; 90:1587–95
36. Negishi C, Lenhardt R, Sessler DI, De Witte J, Ikeda T, Kurz A, Lobo E: Desflurane reduces the febrile response to administration of interleukin-2. *ANESTHESIOLOGY* 1998; 88:1162–9
37. Negishi C, Kim JS, Lenhardt R, Sessler DI, Ozaki M, Vuong K, Bastanmehr H, Bjorksten AR: Alfentanil reduces the febrile response to interleukin-2 in humans. *Crit Care Med* 2000; 28:1295–300
38. Mokhtarani M, Mahgoub AN, Morioka N, Doufas AG, Dae M, Shaughnessy TE, Bjorksten AR, Sessler DI: Buspirone and meperidine synergistically reduce the shivering threshold. *Anesth Analg* 2001; 93:1233–9
39. Doufas AG, Lin CM, Suleman MI, Liem EB, Lenhardt R, Morioka N, Akça O, Shah YM, Bjorksten AR, Sessler DI: Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. *Stroke* 2003; 34:1218–23
40. Alfonsi P, Passard A, Gaude-Joindreau V, Guignard B, Sessler DI, Chauvin M: Nefopam and alfentanil additively reduce the shivering threshold in humans whereas nefopam and clonidine do not. *ANESTHESIOLOGY* 2009; 111:102–9
41. Pagel PS, Hudetz JA: Recent trends in publication of basic science and clinical research by United States investigators in anesthesia journals. *BMC Anesthesiol* 2012; 12:5