SciForschen
Open HUB for Scientific Research

ISSN 2379-7150

Journal of Neurology and Neurobiology

Review Article | Volume: 2.4 | Open Access

Spontaneous Body Temperature Fluctuations in Neurological Patients

Bonnie Wang[1], Martina L Mustroph[2] and Huan Wang[2]*

[1]*Department of Neurology, University of Pennsylvania, Philadelphia, USA*

[2]*Beckman Institute of Advanced Science and Technology, University of Illinois at Urbana-Champaign, Illinois, USA*

***Corresponding author:** Huan Wang, Carle Foundation Hospital, Beckman Institute of Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA, Tel: 2175523425; **E-mail:** John.wang@carle.com

Received date: 07 Jun 2016; **Accepted date:** 06 Jul 2016; **Published date:** 11 Jul 2016.

Citation: Wang B, Mustroph ML, Wang H (2016) Spontaneous Body Temperature Fluctuations in Neurological Patients. J Neurol Neurobiol 2(4): doi http://dx.doi.org/10.16966/2379-7150.127

Abstract

Although body temperature is one of the most tightly regulated homeostatic parameters in humans, temperature abnormalities are frequently encountered in the in-hospital patient population, particularly in those with central nervous system (CNS) pathologies. CNS injuries are a prevalent cause of death and disability in young persons and on the rise among older persons. Brain and body temperature fluctuations in patients with cerebral pathologies are as of yet poorly characterized. The objective of this paper was to review our state of knowledge about spontaneous temperature fluctuations, specifically as they pertain to neurological patients. We provide an overview of the data on spontaneous temperature fluctuations (hyperthermia and hypothermia). 'Is Hotter Better?' evaluates how ambient temperature impacts human thermoregulation and health, reviews therapeutic benefits of induced hyperthermia, and discusses adverse outcomes of spontaneous hypothermia. In 'Is Colder Cooler?,' we review the link between fever and poor outcomes, the detrimental effects of spontaneous hypothermia on mortality, beneficial cerebral effects of spontaneous hypothermia after ischemic brain insult, and the clinical role of therapeutic hypothermia. We conclude that the net effects of early and spontaneous body temperature fluctuations in illness likely depend on the underlying pathological process, specific tissue vulnerabilities towards temperature-induced collateral damage, and the magnitude and duration of spontaneous temperature fluctuations. The paper calls for the community to expand our attention to investigating effects of the entire range of spontaneous body temperature fluctuations in CNS illness, because at present, the therapeutic effect of targeted temperature management in neurological patients remains uncertain.

Keywords: Spontaneous temperature fluctuations; Hyperthermia; Hypothermia; Dysthermia; Neurological patients

Introduction

Endothermy represents a key evolutionary innovation that enables mammals, birds, and a mesopelagic fish (the Opah) to become high-performance predators with fine-tuned neural conductance, faster reaction rates, increased muscle power, and greater capacity for sustained aerobic activity [1,2]. Under various environmental and physiological conditions, endotherms maintain a nearly constant core body temperature (normal daily variation of 0.5°C in humans) but allow other fundamental physiological parameters (respiration, heart rate, blood pressure, etc.) to fluctuate over a much wider range [3,4]. Despite the fact that humans are endotherms, body temperature abnormalities are among the most commonly noted symptoms of in-hospital patient population [5-7]. Central nervous system (CNS) injuries are the leading cause of death and disability in persons aged 15-24 [8]. Severe and acute pathologies affecting the CNS are also becoming leading causes of overall disability and death in countries where an increasing percentage of the population is aging [9,10]. Cerebrovascular disease (stroke) alone is currently the 2nd leading cause of death globally [11]. Humans, as endotherms, regulate body temperature within a narrow range centered around a basal mean temperature that varies little in the absence of pathology. Spontaneous temperature fluctuations outside the normal range occur commonly in neurological patients and remain a significant clinical challenge with much uncertainty regarding their biological significance and optimal treatment [6,7,12-19].

Deviations of body temperature from its normal range are so common in systemic inflammation that both fever and hypothermia are symptoms included in all the recent definitions of sepsis and related syndromes [20,21]; to date, however, research efforts in the sphere of cerebral pathology have primarily focused on spontaneous body temperature elevations and the development of interventions for hyperthermia. Despite lack of clearly demonstrated clinical benefits [16,17], standard practice and common wisdom endorse treatment of spontaneous temperature elevations in neurological patients [22]; in contrast, spontaneous temperature reductions have undeservingly received much less attention. In this paper, we analyse the current literature and review the present state of knowledge concerning spontaneous body temperature fluctuations in neurological patients with CNS illnesses. Aiming to take account of the entire range of spontaneous body temperature fluctuations in such patients, we first provide a comprehensive overview of data focusing on both ends of the spectrum (hyperthermia and hypothermia) and then discuss the data in greater detail. This paper will not discuss thermodysregulation after spinal cord injury because it involves dysfunction of the peripheral cold/warm receptors, autonomic control, and sweating mechanisms that are beyond the scope of this review.

Overview

Human thermoregulatory physiology involves systemic and complex homeostatic mechanisms. Conceptually, it consists of an afferent sensory limb with both warm-sensitive and cold-sensitive thermoreceptors, a central processing center (the hypothalamus) that controls the thermoregulatory set point, and an efferent response limb that induces appropriate heat preservation or heat loss responses. Heat in humans is generated by electron exchange in mitochondria, mostly in liver, brain, heart, and in skeletal muscle contraction. Endotherms rely on centrally released hormonal uncoupling agents to increase the rate of heat

generation. Uncoupling agents allow protons to escape from the inner mitochondrial membrane, which allows for heat generation in lieu of ATP production. Heat is preserved by peripheral vasoconstriction, muscle contraction (shivering), etc. Heat in humans is lost by convection, conduction, radiation, and evaporation; that is, by peripheral vasodilatation, sweating, etc.

The dynamics of brain-body temperature fluctuations are particularly important in patients with cerebral pathologies but have not yet been well characterized. Under normal circumstances, while brain temperature is higher than core body temperature, the two are tightly correlated [23,24]. In patients with brain injury, there may be dissociation between brain and core body temperature, such that body temperature may not be a reliable surrogate for brain temperature. This dissociation between brain and core body temperature (e.g. brain thermopooling) occurs when cerebral blood flow is insufficient to decrease brain tissue temperature. There is heterogeneity in the brain temperature based on region, a phenomenon that has been referred to as selective brain cooling [25,26]. Brain regions close to the well-ventilated scalp-sinus pathway and the anterior cranial fossa, like the frontal lobes, appear to be relatively protected from states of hyperthermia [26]. However, the majority of studies concerning spontaneous temperature alterations are based on systemic not brain temperature [27,28].

Abnormally elevated temperatures may have infectious [29-32] or non-infectious causes. Non-infectious mechanisms include conditions associated with inflammation (e.g. myocardial infarction, pancreatitis), drug hypersensitivity reactions, neurogenic fever, etc. [33-36], and hyperthermia syndromes (heat stroke, neuroleptic malignant syndrome, adrenal crisis, severe thyrotoxicosis, etc.) [27,28,37-40]. The causes of elevated body temperature fall into two categories: true fever (i.e. hypothalamic set point elevation) and hyperthermia (i.e. normal hypothalamic set point). Hypothermia can be caused by cold exposure, severe infection, endocrine abnormalities, and drug overdose [41-43]. Conceptually, it is important to distinguish between physiologically regulated or dysregulated processes leading to body temperature abnormalities. In a physiological response to acute illness, the normal hypothalamic thermoregulatory set point becomes adjusted, and the hypothalamus maintains homeostasis around this new set point. The subsequent temperature fluctuations are still physiologically regulated by the same mechanisms involved in normal temperature homeostasis. Fever is typically part of a cytokine-mediated systemic inflammatory response syndrome triggered by various infections or a range of non-infectious etiologies (trauma, major surgery, and severe pancreatitis) [30,34,35,44]. It is considered physiologically regulated due to an upward adjustment of the normal hypothalamic thermoregulatory set point [45]. Conversely, hyperthermia seen in conditions like neuroleptic malignant syndrome represents a physiological system failure to balance heat gain and loss while the hypothalamus attempts to maintain thermal homeostasis around a normal temperature set point.

There are several neurological disorders in which dysfunctional thermoregulation are a central feature despite no focal hypothalamic, brainstem, spinal lesions, or autonomic failure [46]. Paroxysmal hypothermia with hyperhidrosis (PHH), multiple sclerosis (MS), and Wernicke encephalopathy are three clinical conditions in which spontaneous episodic hypothermia may occur [46]. PHH entails episodes of hypothermia, with associated pallor, flushing, bradycardia, generalized weakness, ataxia, confusion, paroxysmal hyperthermia (reverse Shapiro syndrome), wide temperature fluctuations, and/or migraines, especially in children [46]. External warming is typically not successful [46]. While PHH is not consistently associated with any structural brain abnormalities, a central theory is that PHH is caused by a low core temperature set point as well as hyper functional sweat response due to impaired voltage-gated potassium channels that normally limit the firing frequency of the warm-sensitive neurons in the preoptic hypothalamic area [46]. While hypothermia episodes in MS are not consistently associated with any structural brain abnormalities, in MS, as in Wernicke encephalopathy, the periaqueductal gray area (PAG), held to be a relay station for cold-response pathways, has been compromised at the same time as hypothermic episodes have been observed clinically [46-48].

Temperature regulation changes in humans with age. For example, older patients do not usually have fevers of the same magnitude as younger patients in response to infection [49,50]. A variety of reasons, including immune senescence and malnutrition, have been cited for the blunted fever response observed in older patients, but it is unclear how the blunted fever response in older patients contributes to outcomes from cerebral pathology in older age [49,50].

Best clinical practice guidelines mandate that thermoregulatory failure-induced body temperature abnormalities (heat stroke, hypothermia from cold exposure, malignant hyperthermia) require prompt, acute, and intensive care to rapidly normalize body temperature. In contrast, the appropriate clinical approach towards spontaneous body temperature fluctuations from physiologically regulated responses to acute illnesses remains a matter of debate. Furthermore, in neurological patients, a clear distinction between regulated versus dysregulated temperature fluctuations is often difficult to discern, particularly because certain CNS pathologies may directly or indirectly compromise hypothalamus function. Dysregulated temperature fluctuations in the form of neurogenic fever occur particularly frequently in patients with subarachnoid hemorrhage, intraventricular bleeds, and traumatic brain injury [51]. While the mechanisms of how CNS injury leads to dysthermia are likely multifold, one favoured mechanism for how neurogenic fever occurs is *via* hypothalamus injury [51]. From a proteomic analysis of hypothalamic injury in heatstroke rats, we know that hypothalamus injury leads to hypothalamic ischemia, apoptosis, and injury as evidenced by upregulation of L-lactate dehydrogenase, blood-brain-brain disruption *via* upregulation of glial fibrillary acidic protein, oxidative stress *via* upregulation of cytosolic dehydrogenase-1, and activated inflammation *via* downregulation of stathmin 1[52].

Is Hotter Better?

The metabolic production and retention of heat to maintain a body temperature above the ambient temperature is energetically expensive. Nevertheless, powerful selective advantages have allowed endotherms to evolve towards a higher and higher body temperature until a balance was reached beyond which any further temperature increase would result in deleterious effects (such as decreased protein stability) out weighing its benefits. The range of body temperatures observed in modern mammals and birds is broadly similar, suggesting a common evolutionary temperature limit that has been driven as high as possible [1].

Thomas Sydenham, the father of English medicine, magisterially stated 300 years ago: 'Fever is a mighty engine which nature brings into this world for the conquest of her enemies' [53]. As a nearly ubiquitous host response to infection, fever may confer a strong survival advantage despite its metabolic cost; conversely, lower body temperatures in patients with infections are associated with an extremely high mortality rate [54]. In the context of CNS infections, a retrospective analysis of 6,396 patients with meningitis and encephalitis suggested that early fever as high as 40.0°C or above was not associated with increased hospital mortality and may be beneficial [7]. In the early part of the 20th century, therapeutic hyperthermia was developed when Nobel laureate Julius Wagner-Jauregg induced fever in patients with neurosyphilis-related progressive paralysis by injecting them with blood from patients with malaria. His work on fever therapy effectively improved the remission rates of such paralysis from 1% to 30% [55]. Subsequently, inducing a hyperthermia of 41.7°C for six

hours in a special heat chamber was shown to cure 81% of gonorrhea cases [56]. Clearly, there is a historical precedent of hyperthermia induction in the medical field in the context of infection. In the context of brain injury, the effect of hyperthermia appears to depend on the type of neurological injury; compared to patients with fever and intracerebral hemorrhage, traumatic brain injury (TBI), or aneurysmal subarachnoid hemorrhage, patients with acute ischemic stroke with fever have the highest mortality risk [57].

As an acute response to infectious illness, spontaneous hypothermia is much less common than fever but it is significantly associated with extreme severity of disease and death [42,58,59]. An association between hypothermia and detrimental clinical outcomes has been identified in trauma patients and in patients undergoing elective surgeries [60]; in fact, hypothermia has been shown to be the most important prognostic factor for poor outcome in a large series of prospective studies of trauma patients [61-63]. In patients with non-infectious cerebral pathologies, early low body temperatures (33 to 36°C) are also associated with poor outcome [64-69].

Is Colder Cooler?

Direct recordings of cerebral temperature in the subdural space and brain parenchyma in patients with a variety of intracranial pathologies after neurological surgery show that no specific cooling mechanism other than heat uptake by arterial blood exists that protects the delicate brain from fever, such that brain temperature is consistently the highest recorded temperature compared to other body sites, in normothermia or in fever [46,70,71]. Hypothermia tends to be well-tolerated by neurons, but according to *in vitro* studies, hyperthermia (exceeding 40°C) adversely affects neurons, glia, endothelial, and epithelial cells [46,72,73]. Indeed, fever has been associated with poor functional outcome in patients after acute ischemic stroke [24,74], intracerebral hemorrhage [75], subarachnoid hemorrhage [76,77], and TBI [78,79]; furthermore, fever has been associated with increased intensive care unit (ICU) length of stay (LOS), hospital LOS, and overall mortality [6,80]. A consistent association between fever and poor outcome was also validated in a comprehensive meta-analysis in patients with brain injury [81].

Incidence of spontaneous hypothermia in brain injury appears to range from 1% [57] to 15% [64] at ICU admission. A penetrating mechanism of TBI, injury severity, and undergoing an exploratory laparotomy before admission are independent risk factors for developing hypothermia [82,83]. Old age, co-morbid conditions, and comatose state are associated with an increased incidence of spontaneous hypothermia in patients with brain injury [57].

Based on the data that fever in brain injured patients is associated with poor outcomes [81], one might expect hypothermia to carry beneficial effects. However, a retrospective review of trauma patients showed that hypothermia on surgical ICU admission is associated with decreased survival [83]. In line with this finding, an analysis of 11,033 patients with severe TBI revealed that hypothermia at hospital admission was associated with a significant increase in mortality risk [84]. In-hospital mortality rates for patients with hypothermia at admission range from 54% to 79% [57]. Trauma patients with hypothermia at hospital admission have adjusted odds ratios for mortality three times higher than patients with normothermia [83,85], and admission hypothermia is an independent risk factor for mortality in trauma patients [85,86]. In one study of body temperature in trauma patients, mortality rate reached 100% when body temperature fell below 32°C [62,83], whereas overall mortality rate in trauma patients was 39% [87]. Taken together, the data indicate that spontaneous hypothermia in trauma patients at admission is associated with increased mortality.

In the animal literature, a small number of studies indicate a therapeutic benefit of spontaneous hypothermia, which appears to preserve brain function by protecting temperature-sensitive brain areas from injury and limiting infarct size after an ischemic event. In one study, spontaneous hypothermia in rats after asphyxia cardiac arrest was associated with decreased mortality and less injury to the temporal cortex, parietal cortex, thalamus, CA1 and CA2 neurons in the hippocampus, subiculum, and cerebellar Purkinje cells than was seen in rats subjected to a controlled normothermia intervention [88]. The neuroprotective effect of spontaneous hypothermia persisted for six weeks [88]. Spontaneous hypothermia also appears to have a protective effect after an ischemic event in the brain. In rats that sustained permanent occlusion of the middle cerebral and transient (60-minute) occlusion of the bilateral carotid arteries to induce cerebral ischemia, spontaneous hypothermia down to 32°C was associated with decreased infarction volume compared to rats in which brain temperature was artificially maintained at 37.5°C and compared to rats in which spontaneous hypothermia was prevented for 40 minutes [89]. In another study, rats with a spontaneous brain temperature decline from 36°C to 31-30°C after a transient ischemic insult to the brain showed no striatal damage and only inconsistent damage to the CA1 neurons in the hippocampus, in contrast to rats in which striatal brain temperature was maintained at 36°C [90]. Spontaneous hypothermia of the brain in response to ischemic insult affects different brain areas differently. For instance, there is evidence that the caudoputamen is extremely temperature-sensitive to temperature increases or decreases of as little as 2°C, whereas the CA1 layer of the hippocampus appears to be temperature-sensitive in a linear rather than the step-wise fashion of the caudoputamen [91]. However, these results come from a study in which body temperatures during ischemic brain insult were maintained at 35°C, 37°C, or 39°C. It is unclear whether the differential neuronal temperature vulnerabilities of brain areas like the caudoputamen and CA1 layer of the hippocampus are identical in spontaneous as opposed to induced hypothermia.

In the clinical literature, a small number of studies indicate a therapeutic benefit of spontaneous hypothermia after asphyxia cardiac arrest [88], cerebral ischemia [89], and transient ischemic insult [90]. Therapeutic hypothermia has well-established clinical roles in ischemic brain injury due to cardiac arrest [92-96] and hypoxic ischemic neonatal encephalopathy [97,98]. In order to be therapeutic after cardiac arrest, induced hypothermia need not be extreme; in fact, a multi-center, international, randomized controlled trial in thirty-six ICUs in Europe and Australia showed that mild induced hypothermia (36°C) after the cardiac event has similar outcomes on neurological function after 180 days as moderate induced hypothermia (33°C) [93]. Another trial showed that therapeutic hypothermia with a target temperature <34°C suffices for favorable neurological outcomes post-cardiac arrest [94]. However, induced hypothermia is not a panacea. While mild hypothermia after cardiac arrest is significantly associated with good neurological recovery in most patients, mild hypothermia after cardiac arrest in patients with diabetes mellitus is actually detrimental to neurological recovery and survival outcomes [99]. More recent data suggest that normothermia (36°C) yields similar outcomes as hypothermia after cardiac arrest, which suggests that it is avoidance of fever, and not hypothermia, that is neuroprotective [95].

The role of therapeutic hypothermia in acute stroke has been investigated in several studies. A meta-analysis of 101 publications and a total of 3353 animals that examined the effect of therapeutic hypothermia after ischemic stroke found that therapeutic hypothermia after ischemic stroke reduces infarct size by 44% and neurobehavioral outcomes by 46% [100]. From a study on mice that underwent global cerebral ischemia by bilateral carotid artery occlusion with or without therapeutic hypothermia, it appears that the mechanism of hypothermia that limits infarct size is mitigating the ischemia-induced increase extracellular calcium-sensing receptors and the ischemia-induced decrease in gamma-aminobutyric acid-1B receptors (GABA-1B receptors), an effect that was particularly prominent

in the temperature-sensitive hippocampus [101]. A study of 390 acute stroke patients in Copenhagen showed that patients with hypothermia at admission had less severe strokes and lower mortality rates [12]. The Nordic Cooling Stroke Study (NOCSS), the most ambitious human randomized clinical trial assessing effects of hypothermia in acute stroke to date, intended to test the effect of temperature reduction to 35°C, but was terminated because of slow recruitment [100,102]. The NIH-funded Intravascular Cooling in the Treatment of Stroke-Longer tPA window (ICTuS-L) study tested the combination of hypothermia and intravenous tPA in acute ischemic stroke and found endovascular hypothermia after stroke with intravenous thrombolysis to be preliminarily safe but raised concerns about increased incidence of pneumonia [103,104] and decreased urine output [105] from therapeutic hypothermia. Currently, there is an ongoing European multi-center, randomized phase 3 clinical trial of therapeutic hypothermia plus best medical treatment in patients with acute ischemic stroke [106,107].

In TBI, therapeutic hypothermia has no demonstrated benefits and may be harmful. A prospective multi-center randomized trial of therapeutic hypothermia in severe TBI found that prophylactic hypothermia does not improve survival rates or functional outcomes but increases rates of complications, even though fewer patients in the hypothermia group had high intracranial pressure than in the normothermia group [65,108]. Three of four meta-analyses on therapeutic hypothermia after TBI found no benefit from therapeutic hypothermia [108-112]. Another meta-analysis found that only Asian but not American population's show decreased mortality from prophylactic hypothermia [113]. The Brain Hypothermia study (BHYPO), a multi-center randomized controlled trial of severe TBI patients, found no beneficial effects of prophylactic therapeutic hypothermia on TBI; only in young patients (≤ 50) with evacuated mass lesions did therapeutic hypothermia increase favourable outcomes [114,115]. A recent randomized controlled trial of mild therapeutic hypothermia that improved upon limitations of previous studies found no improvements in neurological outcomes or mortality from prophylactic therapeutic hypothermia for severe TBI [116]. A multi-center international trial of therapeutic hypothermia in children with severe TBI found that therapeutic hypothermia does not improve neurologic outcomes and may in fact increase mortality [108]. Another study of children with TBI in all eight PICUs in Australia and New Zealand and one PICU in Canada found no difference in outcomes at 12 months after injury from prophylactic hypothermia compared to normothermia [117]. A multi-center randomized controlled trial of prophylactic hypothermia in TBI (POLAR trial) at sites in Australia, New Zealand, and Europe is currently underway [118]. The National Acute Brain Injury Study-Hypothermia (NABIS-H) and National Acute Brain Injury Study-Hypothermia II (NABIS-II) studies evaluated whether cooling before evacuation of traumatic intracranial hematomas protects against brain reperfusion injury and whether cooling before and after craniotomy was associated with improved outcomes [119,120]. The NABIS-H I study found some improvement in outcome of patients with hematomas and severe brain injury [119]. However, the NABIS-H II study did not show utility of hypothermia as a neuroprotective intervention for TBI; in fact, the NABIS-H II study was terminated early due to futility [120]. The recent Eurotherm study of therapeutic hypothermia (to 32°C-35°C) for intracranial pressure reduction after TBI was suspended out of safety concerns. Therapeutic hypothermia for patients with intracranial pressure over 20 mm Hg after TBI did not result in superior outcomes compared to standard treatment [121].

While a recent review of studies of a total of 1219 patients undergoing neurosurgery for a variety of reasons (from craniotomies for severe TBI to cerebral aneurysm clipping to hemicraniectomy for edema after cerebral infarction) found no harmful effects from induced hypothermia (32.5°C to 35.0°C), it also found no evidence that induced hypothermia significantly reduced neurological disability or mortality [122]. Normothermia (36.5°C to 38.0°C) appears to be just as safe as hypothermia in neurological surgery.

Dysthermia: Is it Best Not to Be Too Hot or Too Cold?

Intuitively, most clinicians know that extreme spontaneous body temperature fluctuations, either too low or too high (dysthermia), are harmful. In a rabbit model of bacterial infections, the greatest chance of survival correlated with a mild fever compared to either normothermia or a high fever [123]. Similarly, in humans, a retrospective cohort study (n=636,051) involving more than 300 ICUs in Australia, New Zealand, and the UK demonstrated that the lowest risk of death for patients with infection in the first 24 hours occurred at a peak temperature between 39°C–39.4°C [124]. Outside of the context of infection, both spontaneous hypothermia and fever after brain injury appear to confer a greater mortality risk than normothermia upon ICU admission [57]. In the context of cerebral pathologies, a retrospective cohort study of 45,038 patients with TBI or stroke demonstrated that early temperature below 37°C and above 39°C was associated with increased mortality [7]. In a prospective study of severe TBI patients, early temperature outside of the range of 36.5°C to 38°C was associated with a higher probability of death and poorer neurological outcome at 3-month follow-up [19].

Conclusions

Body temperature is one of the most tightly regulated homeostatic parameters in humans, but temperature abnormalities are frequently encountered in neurologically ill patients [6]. The net effects of early and spontaneous body temperature fluctuations associated with neurological illness likely depend on the underlying pathological process (e.g. infectious versus noninfectious), the physiology condition of patients (e.g. young TBI versus elderly stroke patients), the specific tissue vulnerabilities towards collateral injuries induced by temperature changes (e.g. CNS versus other organ systems), and magnitude and duration of temperature fluctuations.

It is crucial to expand our clinical attention and research efforts to investigate the biological effects of the entire range of spontaneous body temperature fluctuations associated with CNS illnesses, particularly hypothermia. The CNS is particularly sensitive to temperature changes [23,24], and early and spontaneous brain and body temperature abnormalities are commonly observed in neurological patients [6]; therefore, temperature, as an independent therapeutic target variable, measurable even in the brain by noninvasive, indirect means such as tympanic temperature [46,125,126], warrants intense clinical attention. Collectively, available data do not yet define a clear framework for understanding how temperature fluctuations impact clinical outcomes. In addition, the therapeutic efficacy of targeted temperature management remains uncertain.

References

1. Clarke A, Portner HO (2010) Temperature, metabolic power and the evolution of endothermy. Biol Rev Camb Philos Soc 85: 703-727.
2. Wegner NC, Snodgrass OE, Dewar H, Hyde JR (2015) Animal physiology. Whole-body endothermy in a mesopelagic fish, the opah, Lampris guttatus. Science 348: 786-789.
3. Bicego KC, Barros RC, Branco LG (2007) Physiology of temperature regulation: comparative aspects. Comp Biochem Physiol A Mol Integr Physiol 147: 616-639.
4. Crawshaw L, Grahn D, Wollmuth L, Simpson L (1985) Central nervous regulation of body temperature in vertebrates: comparative aspects. Pharmacol Ther 30: 19-30.
5. Kushimoto S, Yamanouchi S, Endo T, Sato T, Nomura R, et al. (2014) Body temperature abnormalities in non-neurological critically ill patients: a review of the literature. J Intensive Care 2: 14.

6. Rincon F, Patel U, Schorr C, Lee E, Ross S, et al. (2015) Brain injury as a risk factor for fever upon admission to the intensive care unit and association with in-hospital case fatality: a matched cohort study. J Intensive Care Med 30: 107-114.

7. Saxena M, Young P, Pilcher D, Bailey M, Harrison D, et al. (2015) Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. Intensive Care Med 41: 823-832.

8. Forkosch JA, Kaye HS, Hurman DJ (1994) Incidence of traumatic brain injury in the United States. Disability Statistics Abstract Number 14, U.S. Department of Education, Washington, DC, USA.

9. Faul M, Coronado V (2015) Epidemiology of traumatic brain injury. Handbook of clinical neurology 127: 3-13.

10. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. (2013) Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 127: e6-e245.

11. Mathers C, Fat DM, Boerma JT, WHO (2008) The global burden of disease: 2004 update. World Health Organization, Geneva, Switzerland.

12. Kammersgaard LP, Jørgensen HS, Rungby JA, Reith J, Nakayama H, et al. (2002) Admission body temperature predicts long-term mortality after acute stroke: the Copenhagen Stroke Study. Stroke 33: 1759-1762.

13. Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, et al. (2015) Mortality risk attributable to high and low ambient temperature: a multicountry observational study. The Lancet 386: 369-375.

14. Kim SH, Saver JL (2015) Initial body temperature in ischemic stroke: nonpotentiation of tissue-type plasminogen activator benefit and inverse association with severity. Stroke 46: 132-136.

15. Kirkness CJ, Burr RL, Thompson HJ, Mitchell PH (2008) Temperature rhythm in aneurysmal subarachnoid hemorrhage. Neurocrit Care 8: 380-390.

16. Lord AS, Karinja S, Lantigua H, Carpenter A, Schmidt JM, et al. (2014) Therapeutic temperature modulation for fever after intracerebral hemorrhage. Neurocrit Care 21: 200-206

17. Morgenstern LB, Hemphill JC, Anderson C, Becker K, Broderick JP, et al. (2010) Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 41: 2108-2129.

18. Reith J, Jørgensen HS, Pedersen PM, Nakayama H, Raaschou HO, et al. (1996) Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet 347: 422-425.

19. Sacho RH, Vail A, Rainey T, King AT, Childs C (2010) The effect of spontaneous alterations in brain temperature on outcome: a prospective observational cohort study in patients with severe traumatic brain injury. J Neurotrauma 27: 2157-2164.

20. Bone RC (1991) Sepsis, the sepsis syndrome, multi-organ failure: a plea for comparable definitions. Ann Intern Med 114: 332-333.

21. Bone RC, Sprung CL, Sibbald WJ (1992) Definitions for sepsis and organ failure. Critical care medicine 20: 724-726.

22. Rincon F, Mayer SA (2008) Clinical review: Critical care management of spontaneous intracerebral hemorrhage. Crit Care 12: 237.

23. Wang H, Wang B, Normoyle KP, Jackson K, Spitler K, et al. (2014) Brain temperature and its fundamental properties: a review for clinical neuroscientists. Front Neurosci 8: 307.

24. Wang Y, Lim LL, Levi C, Heller RF, Fisher J (2000) Influence of admission body temperature on stroke mortality. Stroke 31: 404-409.

25. Hayashi N (2000) Brain thermo-pooling is the major problem in pediatric influenza encephalitis. No To Hattatsu 32: 156-162.

26. Mrozek S, Vardon F, Geeraerts T (2012) Brain temperature: Physiology and pathophysiology after brain injury. Anesthesiology Research and Practice 2012: 989487.

27. Kothari VM, Karnad DR (2005) New onset fever in the intensive care unit. J Assoc Physicians India 53: 949-953

28. Niven DJ, Leger C, Stelfox HT, Laupland KB (2012) Fever in the critically ill: a review of epidemiology, immunology, and management. J Intensive Care Med 27: 290-297.

29. Bieganska MJ (2014) Two fundamentals of mammalian defense in fungal infections: endothermy and innate antifungal immunity. Pol J Vet Sci 17: 555-567.

30. Gourine AV, Rudolph K, Tesfaigzi J, Kluger MJ (1998) Role of hypothalamic interleukin-1beta in fever induced by cecal ligation and puncture in rats. Am J Physiol 275: R754-761.

31. Mendis KN, Carter R (1992) The role of cytokines in *Plasmodium vivax* malaria. Memorias do Instituto Oswaldo Cruz 3: 51-55.

32. Sahu R, Verma R, Jain A, Garg RK, Singh MK, et al. (2014) Neurologic complications in dengue virus infection: a prospective cohort study. Neurology 83: 1601-1609.

33. Avancini J, Maragno L, Santi CG, Criado PR (2015) Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome: clinical features of 27 patients. Clin Exp Dermatol 40: 851-859.

34. Mathiesen T, Edner G, Ulfarsson E, Andersson B (1997) Cerebrospinal fluid interleukin-1 receptor antagonist and tumor necrosis factor-alpha following subarachnoid hemorrhage. J Neurosurg 87: 215-220.

35. Norman JG (1999) New approaches to acute pancreatitis: role of inflammatory mediators. Digestion 60: 57-60.

36. Risoe C, Kirkeby OJ, Grottum P, Sederholm M, Kjekshus JK (1987) Fever after acute myocardial infarction in patients treated with intravenous timolol or placebo. Br Heart J 57: 28-31.

37. Biedenkapp JC, Leon LR (2013) Increased cytokine and chemokine gene expression in the CNS of mice during heat stroke recovery. Am J Physiol Regul Integr Comp Physiol 305: R978-R986.

38. Shaked Y, Samra Y, Zwas ST (1988) Graves' disease presenting as pyrexia of unknown origin. Postgrad Med J 64: 209-212.

39. Shenker Y, Skatrud JB (2001) Adrenal insufficiency in critically ill patients. American journal of respiratory and critical care medicine 163: 1520-1523.

40. Trollor JN, Chen X, Chitty K, Sachdev PS (2012) Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. Br J Psychiatry 201: 52-56.

41. Brivet F, Carras PM, Dormont J, Guidet B, Offenstadt G, et al. (1994) Hypothermia, a pertinent clinical prognostic factor in severe systemic inflammatory response syndrome. Crit Care Med 22: 533-534.

42. Clemmer TP, Fisher CJ Jr, Bone RC, Slotman GJ, Metz CA, et al. (1992) Hypothermia in the sepsis syndrome and clinical outcome. The Methylprednisolone Severe Sepsis Study Group. Crit Care Med 20: 1395-1401.

43. Megarbane B, Axler O, Chary I, Pompier R, Brivet FG (2000) Hypothermia with indoor occurrence is associated with a worse outcome. Intensive Care Med 26: 1843-1849.

44. Appenheimer MM, Girard RA, Chen Q, Wang WC, Bankert KC, et al. (2007) Conservation of IL-6 trans-signaling mechanisms controlling L-selectin adhesion by fever-range thermal stress. Eur J Immunol 37: 2856-2867.

45. Mackowiak PA (1998) Concepts of fever. Arch Intern Med 158: 1870-1881.

46. Benarroch EE (2007) Thermoregulation: recent concepts and remaining questions. Neurology 69: 1293-1297.

47. Edwards S, Lennox G, Robson K, Whiteley A (1996) Hypothermia due to hypothalamic involvement in multiple sclerosis. J Neurol Neurosurg Psychiatry 61: 419-420.

48. White KD, Scoones DJ, Newman PK (1996) Hypothermia in multiple sclerosis. J Neurol Neurosurg Psychiatry 61: 369-375.

49. Castle SC, Norman DC, Yeh M, Miller D, Yoshikawa TT (1991) Fever response in elderly nursing home residents: are the older truly colder? J Am Geriatr Soc 39: 853-857.

50. Gavazzi G, Krause KH (2002) Ageing and infection. Lancet Infect Dis 2: 659-666.

51. Meier K, Lee K (2016) Neurogenic Fever: Review of pathophysiology, evaluation, and management. J Intensive Care Med.

52. Chao CM, Cheng BC, Chen CY, Lin MT, Chang CP, et al. (2015) Proteomic analysis of hypothalamic injury in heatstroke rats. Proteomics 15: 1921-1934.

53. Atkins E (1985) Fever: historical perspectives and evolution of modern views. Rheumatology 24: 1-5.

54. Kushimoto S, Gando S, Saitoh D, Mayumi T, Ogura H, et al. (2013) The impact of body temperature abnormalities on the disease severity and outcome in patients with severe sepsis: an analysis from a multicenter, prospective survey of severe sepsis. Crit Care 17: R271.

55. Wagner-Jauregg J (1927) The treatment of dementia paralytica by malaria innoculation, Elsevier, New York, USA.

56. Owens CA (1936) The value of fever therapy in gonorrhea. JAMA 107: 1942-1946.

57. Rincon F, Hunter K, Schorr C, Dellinger RP, Zanotti-Cavazzoni S (2014) The epidemiology of spontaneous fever and hypothermia on admission of brain injury patients to intensive care units: a multicenter cohort study. J Neurosurg 121: 950-960.

58. Doherty NE, Fung P, Lefkowitz M, Ellrodt AG (1985) Hypothermia and sepsis. Ann Intern Med 103: 308.

59. Dupont HL, Spink WW (1969) Infections due to gram-negative organisms: an analysis of 860 patients with bacteremia at the University of Minnesota medical center, 1958-1966. Medicine (Baltimore) 48: 307-332.

60. Hildebrand F, Giannoudis PV, van Griensven M, Chawda M, Pape HC (2004) Pathophysiologic changes and effects of hypothermia on outcome in elective surgery and trauma patients. Am J Surg 187: 363-371.

61. Gentilello LM, Jurkovich GJ, Stark MS, Hassantash SA, O'Keefe GE (1997) Is hypothermia in the victim of major trauma protective or harmful? A randomized, prospective study. Ann Surg 226: 439-447.

62. Jurkovich GJ, Greiser WB, Luterman A, Curreri PW (1987) Hypothermia in trauma victims: an ominous predictor of survival. J Trauma 27: 1019-1024.

63. Malone DL, Kuhls D, Napolitano LM, mccarter R, Scalea T (2001) Back to basics: validation of the admission systemic inflammatory response syndrome score in predicting outcome in trauma. J Trauma 51: 458-463.

64. Clifton GL, Miller ER, Choi SC, Levin HS, mccauley S, et al. (2002) Hypothermia on admission in patients with severe brain injury. J Neurotrauma 19: 293-301.

65. Clifton GL, Miller ER, Choi SC, Levin HS, mccauley S, et al. (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344: 556-563.

66. Jeremitsky E, Omert L, Dunham CM, Protetch J, Rodriguez A (2003) Harbingers of poor outcome the day after severe brain injury: hypothermia, hypoxia, and hypoperfusion. J Trauma 54: 312-319.

67. Otawara Y, Ogasawara K, Kubo Y, Tomitsuka N, Ogawa A, et al. (2003) Brain and systemic temperature in patients with severe subarachnoid hemorrhage. Surg Neurol 60: 159-164.

68. Soukup J, Zauner A, Doppenberg EM, Menzel M, Gilman C, et al. (2002) Relationship between brain temperature, brain chemistry and oxygen delivery after severe human head injury: the effect of mild hypothermia. Neurol Res 24: 161-168.

69. Soukup J, Zauner A, Doppenberg EM, Menzel M, Gilman C, et al. (2002) The importance of brain temperature in patients after severe head injury: relationship to intracranial pressure, cerebral perfusion pressure, cerebral blood flow, and outcome. J Neurotrauma 19: 559-571.

70. Mariak Z, Jadeszko M, Lewko J, Lebkowski W, Lyson T (1998) No specific brain protection against thermal stress in fever. Acta Neurochir 140: 585-590.

71. Mariak Z, Lysoń T, Piekarski P, Lewko J, Jadeszko M, et al. (2000) Brain temperature in patients with central nervous system lesions. Neurol Neurochir Pol 34: 509-522.

72. Bechtold DA, Brown IR (2003) Induction of Hsp27 and Hsp32 stress proteins and vimentin in glial cells of the rat hippocampus following hyperthermia. Neurochem Res 28: 1163-1173.

73. Sharma HS, Hoopes PJ (2003) Hyperthermia induced pathophysiology of the central nervous system. Int J Hyperthermia 19: 325-354.

74. Saini M, Saqqur M, Kamruzzaman A, Lees KR, Shuaib A, et al. (2009) Effect of hyperthermia on prognosis after acute ischemic stroke. Stroke 40: 3051-3059.

75. Rincon F, Lyden P, Mayer SA (2013) Relationship between temperature, hematoma growth, and functional outcome after intracerebral hemorrhage. Neurocrit Care 18: 45-53.

76. Fernandez A, Schmidt JM, Claassen J, Pavlicova M, Huddleston D, et al. (2007) Fever after subarachnoid hemorrhage: risk factors and impact on outcome. Neurology 68: 1013-1019.

77. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, et al. (2001) Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology 56: 1299-1304.

78. Rossi S, Zanier ER, Mauri I, Columbo A, Stocchetti N (2001) Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. J Neurol Neurosurg Psychiatry 71: 448-454.

79. Stocchetti N, Rossi S, Zanier ER, Colombo A, Beretta L, et al. (2002) Pyrexia in head-injured patients admitted to intensive care. Intensive Care Med 28: 1555-1562.

80. Diringer MN, Reaven NL, Funk SE, Uman GC (2004) Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med 32: 1489-1495.

81. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC (2008) Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke 39: 3029-3035.

82. Gregory JS, Flancbaum L, Townsend MC, Cloutier CT, Jonasson O (1991) Incidence and timing of hypothermia in trauma patients undergoing operations. J Trauma 31: 795-798.

83. Konstantinidis A, Inaba K, Dubose J, Barmparas G, Talving P, et al. (2011) The impact of nontherapeutic hypothermia on outcomes after severe traumatic brain injury. J Trauma 71: 1627-1631.

84. Rubiano AM, Sanchez AI, Estebanez G, Peitzman A, Sperry J, et al. (2013) The effect of admission spontaneous hypothermia on patients with severe traumatic brain injury. Injury 44: 1219-1225.

85. Wang HE, Callaway CW, Peitzman AB, Tisherman SA (2005) Admission hypothermia and outcome after major trauma. Crit Care Med 33: 1296-1301.

86. Shafi S, Elliott AC, Gentilello L (2005) Is hypothermia simply a marker of shock and injury severity or an independent risk factor for mortality in trauma patients? Analysis of a large national trauma registry. J Trauma 59: 1081-1085.

87. Martin RS, Kilgo PD, Miller PR, Hoth JJ, Meredith JW, et al. (2005) Injury-associated hypothermia: an analysis of the 2004 National Trauma Data Bank. Shock 24: 114-118.

88. Hickey RW, Ferimer H, Alexander HL, Garman RH, Callaway CW, et al. (2000) Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats. Crit Care Med 28: 3511-3516.

89. Moyer DJ, Welsh FA, Zager EL (1992) Spontaneous cerebral hypothermia diminishes focal infarction in rat brain. Stroke 23: 1812-1816.

90. Busto R, Dietrich WD, Globus MY, Valdés I, Scheinberg P, et al. (1987) Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7: 729-738.

91. Minamisawa H, Nordstrom CH, Smith ML, Siesjo BK (1990) The influence of mild body and brain hypothermia on ischemic brain damage. J Cereb Blood Flow Metab 10: 365-374.

92. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, et al. (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346: 557-563.

93. Chandrasekaran PN, Dezfulian C, Polderman KH (2015) What is the right temperature to cool post-cardiac arrest patients?, Crit Care 19: 406.

94. Kaneko T, Kasaoka S, Nakahara T, Sawano H, Tahara Y, et al. (2015) Effectiveness of lower target temperature therapeutic hypothermia in post-cardiac arrest syndrome patients with a resuscitation interval of ≤ 30 min. J Intensive Care 3: 28.

95. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, et al. (2013) Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 369: 2197-2206.

96. Safar PJ, Kochanek PM (2002) Therapeutic hypothermia after cardiac arrest, N Engl J Med 346: 612-613.

97. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, et al. (2005) Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 365: 663-670.

98. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, mcdonald SA, et al. (2005) Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 353: 1574-1584.

99. Ro YS, Shin SD, Song KJ, Lee EJ, Lee YJ, et al. (2015) Interaction effects between hypothermia and diabetes mellitus on survival outcomes after out-of-hospital cardiac arrest. Resuscitation 90: 35-41.

100. Van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR (2007) Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. Brain 130: 3063-3074.

101. Kim JY, Kim N, Yenari MA, Chang W (2011) Mild Hypothermia Suppresses Calcium-Sensing Receptor (casr) Induction Following Forebrain Ischemia While Increasing GABA-B Receptor 1 (GABA-B-R1) Expression. Transl Stroke Res 2: 195-201.

102. Olsen TS, Weber UJ, Kammersgaard LP (2003) Therapeutic hypothermia for acute stroke. Lancet Neurol 2: 410–416.

103. Guluma KZ, Hemmen TM, Olsen SE, Rapp KS, Lyden PD (2006) A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: methodology. Acad Emerg Med 13: 820-827.

104. Hemmen TM, Raman R, Guluma KZ, Meyer BC, Gomes JA, et al. (2010) Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ictus-L): final results. Stroke 41: 2265-2270.

105. Guluma KZ, Liu L, Hemmen TM, Acharya AB, Rapp KS, et al. (2010) Therapeutic hypothermia is associated with a decrease in urine output in acute stroke patients. Resuscitation 81: 1642-1647.

106. Lyden PD, Rincon F, Staykov D (2015) Clinical studies targeting stroke. Ther Hypothermia Temp Manag 5: 4-8.

107. Van der Worp HB, Macleod MR, Bath PM, Demotes J, Durand-Zaleski I, et al. (2014) eurohyp-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. Best medical treatment alone for acute ischemic stroke. Int J Stroke 9: 642-645.

108. Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, et al. (2008) Hypothermia therapy after traumatic brain injury in children. N Engl J Med 358: 2447-2456.

109. Alderson P, Gadkary C, Signorini DF (2004) Therapeutic hypothermia for head injury. Cochrane Database Syst Rev 18: CD001048.

110. Harris OA, Colford JM, Good MC, Matz PG (2002) The role of hypothermia in the management of severe brain injury: a meta-analysis. Arch Neurol 59: 1077-1083.

111. Henderson WR, Dhingra VK, Chittock DR, Fenwick JC, Ronco JJ (2003) Hypothermia in the management of traumatic brain injury. A systematic review and meta-analysis, Intensive care med 29: 1637-1644.

112. Mcintyre LA, Fergusson DA, Hebert PC, Moher D, Hutchison JS (2003) Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. JAMA 289: 2992-2999.

113. Li P,Yang C (2014) Moderate hypothermia treatment in adult patients with severe traumatic brain injury: a meta-analysis. Brain inj 28: 1036-1041.

114. Hifumi T, Kuroda Y, Kawakita K, Yamashita S, Oda Y, et al. (2015) Fever control management is preferable to mild therapeutic hypothermia in traumatic brain injury patients with abbreviated injury scale 3-4: a multi-center, randomized controlled trial. J Neurotrauma 33: 1047-1053.

115. Suehiro E, Koizumi H, Fujisawa H, Fujita M, Kaneko T, et al. (2015) Diverse effects of hypothermia therapy in patients with severe traumatic brain injury based on the computed tomography classification of the traumatic coma data bank. J Neurotrauma 32: 353-358.

116. Maekawa T, Yamashita S, Nagao S, Hayashi N, Ohashi Y (2015) Prolonged mild therapeutic hypothermia versus fever control with tight hemodynamic monitoring and slow rewarming in patients with severe traumatic brain injury: a randomized controlled trial. J neurotrauma 32: 422-429.

117. Beca J, mcsharry B, Erickson S, Yung M, Schibler A, et al. (2015) Hypothermia for traumatic brain injury in children-a phase II randomized controlled trial. Crit Care Med 43: 1458-1466.

118. Nichol A, Gantner D, Presneill J, Murray L, Trapani T, et al. (2015) Protocol for a multicentre randomised controlled trial of early and sustained prophylactic hypothermia in the management of traumatic brain injury. Crit Care Resusc 17: 92-100.

119. Clifton GL, Coffey CS, Fourwinds S, Zygun D, Valadka A, et al. (2012) Early induction of hypothermia for evacuated intracranial hematomas: a post hoc analysis of two clinical trials. J neurosurg 117: 714-720.

120. Clifton GL, Valadka A, Zygun D, Coffey CS, Drever P, et al. (2011) Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. Lancet Neurol 10: 131-139.

121. Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG, et al. (2015) Hypothermia for intracranial hypertension after traumatic brain injury. N Engl J Med 373: 2403-2412.

122. Galvin IM, Levy R, Boyd JG, Day AG, Wallace MC (2015) Cooling for cerebral protection during brain surgery. Cochrane Database Syst Rev 1: CD006638.

123. Kluger MJ, Vaughn LK (1978) Fever and survival in rabbits infected with Pasteurella multocida. J Physiol 282: 243-251.

124. Young PJ, Saxena M, Beasley R, Bellomo R, Bailey M, et al. (2012) Early peak temperature and mortality in critically ill patients with or without infection. Intensive Care Med.

125. Brinnel H, Nagasaka T, Cabanac M (1987) Enhanced brain protection during passive hyperthermia in humans. Eur J Appl Physiol Occup Physiol 56: 540-545.

126. Cabanac M, Germain M, Brinnel H (1987) Tympanic temperatures during hemiface cooling. Eur J Appl Physiol Occup Physiol 56: 534-539.