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neurocritical care society Neurocrit Care (2011) 15:107–112
DOI 10.1007/s12028-010-9451-1

ORIGINAL ARTICLE

Treatment of Resistant Fever: New Method of Local Cerebral Cooling

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Published online: 1 October 2010
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Abstract
Background Fever in neurocritical care patients is common and has a negative impact on neurological outcome. The purpose of this prospective observational study was (1) to evaluate the practicability of cooling with newly developed neck pads in the daily setting of neurointensive care unit (NICU) patients and (2) to evaluate its effectiveness as a surrogate endpoint to indicate the feasibility of neck cooling as a new method for intractable fever.
Methods Nine patients with ten episodes of intractable fever and aneurysmal subarachnoid hemorrhage were treated with one of two different shapes of specifically adapted cooling neck pads. Temperature values of the brain, blood, and urinary bladder were taken close meshed after application of the cooling neck pads up to hour 8.
Results The brain, blood, and urinary bladder temperatures decreased significantly from hour 0 to a minimum in hour 5 ($P < 0.01$). After hour 5, instead of continuous cooling in all the patients, the temperature of all the three sites remounted.
Conclusion This study showed the practicability of local cooling for intractable fever using the newly developed neck pads in the daily setting of NICU patients.

Keywords Fever · Local cooling · Neck pads · SAH · Brain temperature · Heat transfer coefficient

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Introduction

Fever occurs with an incidence of up to 70% in neurologically injured patients. To reduce fever-related secondary brain damage and to improve clinical outcome, the temperature of the brain needs to be monitored and strictly controlled [1–7]. One of the key centers of thermoregulation of the human body represents the medial preoptic anterior hypothalamic area (POA), influenced by multiple thermoreceptors, feed forward reflex pathways, feedback mechanisms, and pyrogenic mediators [1, 7–11]. Furthermore, the POA is supplied by dendrites ending in the third ventricle and getting information of all the ascending thermoreceptive, pathways as well as endogenous signals in the cerebrospinal fluid [8, 9] (Fig. 1).

There are various possibilities to intervene in this thermoregulation by external devices. Compared to an intravascular cooling method, which is efficient and fast, but invasive and with several relevant side effects such as venous thrombosis or cause of infections, the advantage of a local cooling device becomes obvious. For specific cooling of the deep brain, head caps are not efficient

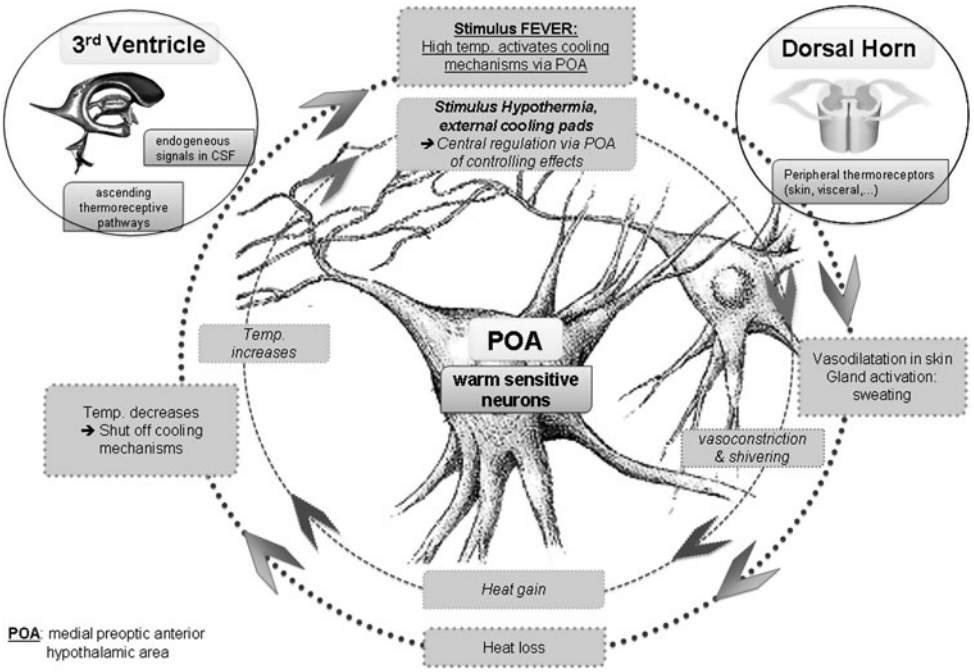

Fig. 1 Simplified cascade of thermoregulatory pathways

[12–14], whereas neck pads covering bilateral the carotid triangle decrease the brain temperature in a mathematical simulation [13, 15]. In a previous study, we simulated cerebral temperature behavior by applying different cooling devices [13]. They simulated cerebral temperature behavior with hypothermia treatment applying different cooling devices. The models were based on hourly temperature values recorded in patients with severe aneurysmal subarachnoid hemorrhage (aSAH), taking into account magnetic resonance imaging data, thermal conductive properties, metabolism, and blood flow, and were applied to different scenarios of hypothermia. In summary, systemic hypothermia by endovascular cooling leads to a uniform temperature decrease within the brain tissue. Cooling with head caps lead to 33°C only in the superficial brain, while the deep brain remains higher than 36°C. In contrast cooling with neck pads, covering the carotid triangles, lead to 35.8°C for dry, and 32.8°C for wet skin in the deep brain within 6 h. The equation of the mathematical model included temperature-dependent blood perfusion, cerebral metabolic rate, and time-dependent arterial blood temperature [13].

These findings encouraged us to create new shapes of cooling devices for selective cooling of the carotid triangles to attempt to decrease the brain temperature in patients with fever resisting conventional methods. The purpose of this observational study was to evaluate the practicability of cooling with newly developed neck pads in the daily setting of neurointensive care unit (NICU) patients and its effectiveness as a surrogate endpoint to indicate the feasibility of neck cooling as a new method for intractable fever.

Methods

This prospective study was approved by the local ethics committee and followed institutional guidelines.

Two shapes of neck pads for covering the carotid triangles with a contact surface as large as possible have been developed. These neck pads were effective in cooling the blood inflow within the carotid arteries neither limiting the patient care and comfort nor venous drainage. The first shape was created for standard-sized necks. The second shape of the neck pads was created to fit patients with a short neck or a tracheostoma, with a smaller width in general and above all in the middle section (Fig. 2a, b). Corresponding to our mathematical simulations, the heat transfer coefficient (htc) in these pads was about 22.4 watts per meter squared-kelvin ($W/(m^2K)$) with a mathematical optimal htc of 28 $W/(m^2K)$. Tissue density, tissue specific heat coefficients, blood perfusion rate, heat source of the natural metabolism, and further values were implemented in the mathematical equation representing the thermal behavior of the different tissues and blood, which was developed in the previous study [13] and transferred in this practical observational study. The ArcticSun® Temperature Management System (Medivance, Louisville CO) was used, employing hydrogel-coated water-circulating energy transfer pads to allow an intimate adhesion to the patient's skin and a similar heat exchange coefficient as in a water bath [16]. The cooling system was set to the automatic mode with the desired patient target temperature of 36.8°C working continuously with maximal cooling capacity. The lowest water temperature was 5°C. The water flow

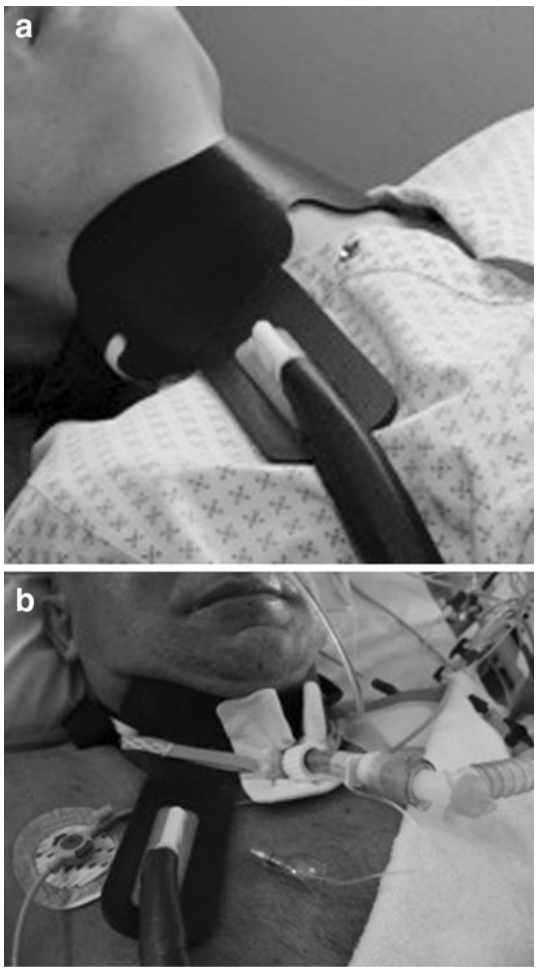

Fig. 2 Cooling neck pads with afferent and efferent suction of cool water from the right side. **a** regular shape **b** shape for short necks and/or tracheostoma

through the neck pads was accelerated by a shunt-line parallel to the neck pad flow, resulting in a continuous flow between 1.7 l/min and 2.3 l/min.

Inclusion criteria of our nine consecutive patients were having a brain temperature probe and presenting episodes of intractable fever ($n = 10$) within 4 weeks after aSAH. Patient demographics are summarized in Table 1. Our standard treatment protocol of patients with aSAH is described by Lerch et al. [17]. Each patient was treated with one of the specific neck pads. Intractable fever was defined as a temperature $>37.8°$ persistent after 2 h of expanded standard fever management with application of acetaminophen (1 gm every 6 h), novaminsulfone (1 gm every 6 h), specific washing solutions (mixture of yellow lemon, bergamot, cajeput oil, star eucalyptus, added by water), and ice packs (inguinal).

Overall 459 temperature values of the brain (Tbrain), blood (Tblood), and urinary bladder (Tbladder) were taken every 15 min over a period of 2 h, every 30 min until hour 4 and hourly up to hour 8, after application of the cooling neck pads. Tbrain was continuously recorded via a thermistor embedded in the ventricular drainage (Neurovent-P Temp, Raumedic®), in addition to continuous temperature measurement of the arterial blood (Pulsiocath Thermodilution catheter, Pulsion Medical Systems AG) and the urinary bladder via indwelling catheter (Foley Catheter with temperature sensor, Curity, Kendall, tyco Healthcare).

Table 1 Patient demographics

Female	4
Male	5
Age (years)	48.7 ± 9
Hunt & Hess	3.3 ± 1.0
Fisher Grade	3.4 ± 0.5
WFNS	3.2 ± 1.6
Clipping	4
Coiling	5
Fever post-SAH (days)	8.3 ± 5.9
Infection	8
Central fever	2
Vigilance on "neck pad day"	
GCS ≥ 13	1
Comatose	8
Analgosedation	7
Fentanyl	5
Midazolam	5
Thiopental	1
Propofol	2
Spontaneous breathing	2
Artificial ventilation	7
Oral intubation	5
Tracheostoma	3

Patients with remounting temperatures after the 8 h of applied neck pads were treated either by adding leg or body pads of the ArcticSun® system or by placing an intravascular cooling system.

All the patients were monitored carefully for possible side effects related to the application of the neck pads. Side effects were defined as skin irritation, pressure marks, wound infection, disturbances in wound healing of a new tracheostomy, or shivering. Shivering, defined as involuntary, oscillatory muscular activity, and cutaneous vasoconstriction [18] was assessed together with each taken temperature value at fixed times as mentioned above and documented as absent, mild, or severe. Changes of the analgetic or sedative medication, changes in arterial blood pressure, and heart rate were documented at least hourly following the standard treatment protocol.

Temperature values are given in mean °C ± standard deviation. All the temperature values of the three

compartments before and after cooling, as well as the temperature values between brain, blood, and urinary bladder were compared using a paired Wilcoxon Mann–Whitney *U*-test.

Results

The brain temperature decreased significantly after 5 h with neck pad cooling from 38.2 ± 0.3 (hour 0) to a minimum of 37.7 ± 0.3 (hour 5) ($P < 0.01$). Comparably Tblood and Tbladder decreased significantly from hour 0 to a minimum in hour 5 from 38.1 ± 0.3 to 37.7 ± 0.2 and from 38.3 ± 0.4 to 37.8 ± 0.3, respectively ($P < 0.01$). After hour 5, instead of continuous cooling, in all the patients the temperature of the brain remounted (Fig. 3).

The cooling system was set to the automatic mode maintaining 5°C after achievement of steady-state status during the study period in all the patients.

In eight fever episodes of seven patients the performed standard methods in fixed intervals for lowering temperature (see above) were continued during the neck pad application without any systematic lasting decline in temperature (38.1 ± 0.4 before medicaments ($n = 8$) or washing ($n = 4$), respectively, and 38.0 ± 0.3 after 1 hour of one of these interventions; ($n = 12$)).

No shivering and no side effects as defined above related to the neck pad cooling technique occurred. Furthermore, no increase of ICP as a potential worsening of jugular venous drainage occurred, no related changes in blood pressure or heart rate were observed, and a tracheostoma was not debilitating. The analgosedation of the patients

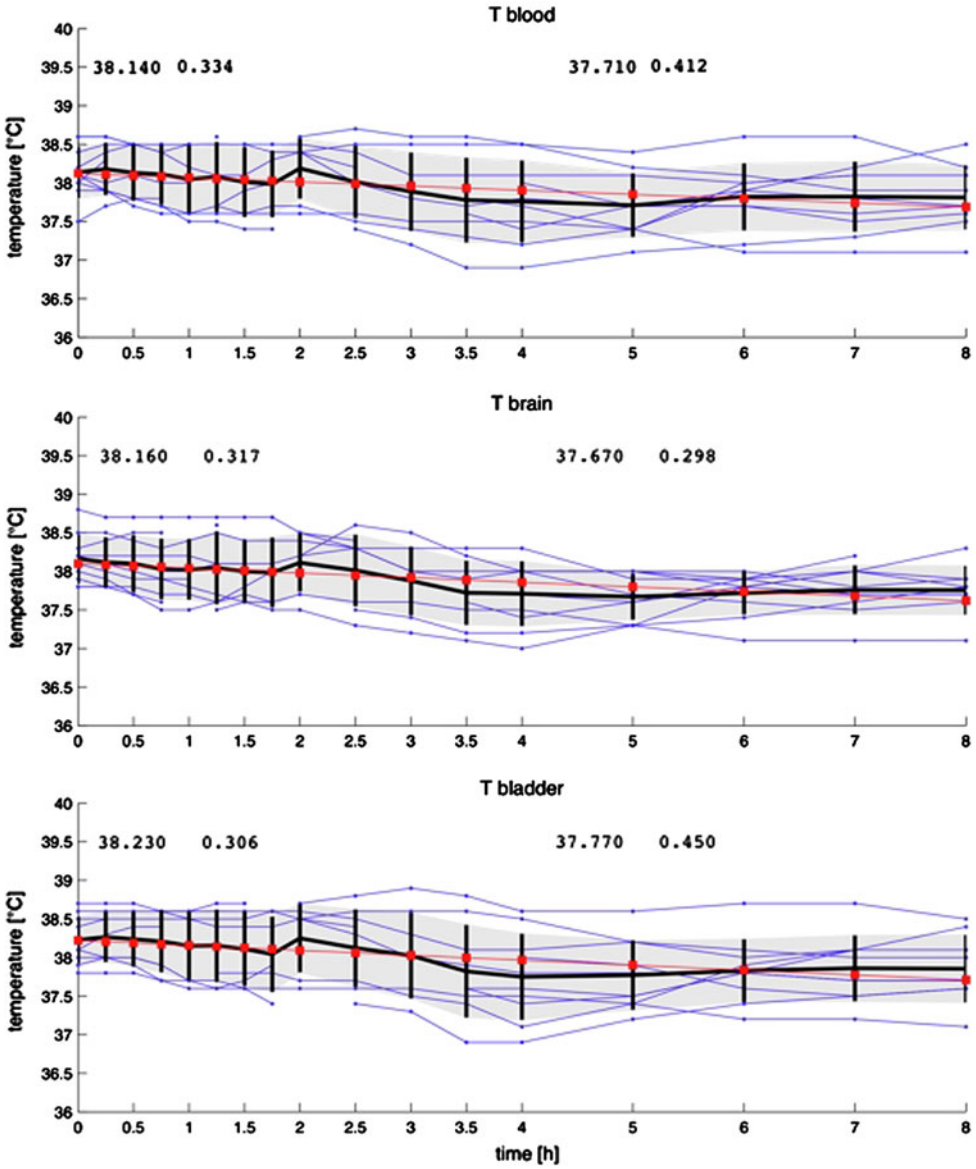

Fig. 3 Three diagrams showing the data of all the temperatures (T in °C) taken in the blood, brain, or urinary bladder over a period of 8 h after application of the neck pad device, with shorter time intervals at the beginning. *Bold black line* and *bars*: *Bold line* represents the mean of the temperatures, the *bars* demonstrate the mean ± standard deviation from hour 0 (before application of the neck pad cooling) to hour 8 (after start of the neck pad cooling). *Fine lines*: Each fine *blue line* represents one fever episode with each registered value before (hour 0) and after application of the neck pad (until hour 8). The *red line* represents the median. *Numbers above each diagram from the left to the right*: Mean hour 0 and standard deviation Mean hour 5 and standard deviation

ranged between deep comatose and awake with slight analgosedation (Table 1). No change of analgosedation was performed during the study period.

Discussion

Choosing patients with aneurysmal subarachnoid hemorrhage, provides a group of patients at high risk for fever, who are most difficult to treat [1]. After application of various antipyretics and cool washing solutions the neck pads could significantly decrease the temperature of the brain, blood, and urinary bladder, respectively. Although the cooling result was significant, the amount of temperature decrease was small. We studied nine consecutive patients with intractable fever with random neck sizes and created two shapes of neck pad devices, to achieve a more flexible fit to the various neck types. The neck pads were applicable in every neck constitution of our patients.

We observed no side effects and no shivering as defined in the method section. Possible explanations for the lack of shivering in our patient group might be the small covered area by the neck pads, the small amount of temperature decline and analgosedation in most of the patients. Furthermore, in all our patients serum magnesium levels were close to the upper limit [18], following our standard treatment protocol of aSAH [17]. Despite concerns of an accidental obstruction of the jugular venous drainage or triggering of autonomous dysfunctions via vulnerable structures like the glossopharyngeal and vagal nerves or carotid bodies, we did not observe any relevant changes concerning these issues during the study period after application of the neck pads. Applying the neck pads as local cooling devices, one should keep in mind that it seems to present not only local, but also systemic hypothermic effects. This could also be assumed by our results of simultaneous behavior of the temperatures in all the three locations (brain, urinary bladder, blood) and might be associated with systemic side effects.

Illustrated in Fig. 3, there are two episodes of remounting temperatures. Regarding the short-term temperature increase in our patients after the same delay time after the start of the neck pad device application, spontaneous fever variations seem to be unlikely. The hypothesis of a counterregulation provoked by treatment of fever was discussed by Keller et al. [13] based on the mathematical models. The origin and mechanisms of thermoregulation of brain and body are very complex and the exact causes of set-point changes are discussed controversially [19–21]. Performing a kind of interval cooling to avoid or reduce triggering of potential counterregulation could be an alternative approach to attempt to extend the period of normalized brain temperature. But it would be very difficult to define the most efficient on-/off-time episodes for cooling, as well as the consideration of all the unstable components. To the best of our knowledge, there is no mathematical model to simulate the reaction of fever treatment and counterregulation. In eight of ten fever episodes the patients received additional applications to the cooling neck pads, such as acetaminophen, novaminsulfone or specific washing, independently of the first early remount of temperature. The antipyretics were given in standardized fixed intervals and continued as analgetic drugs when it came to the decision to apply the neck pads. We inspected the temperature values across the whole range during each of the 12 washing and pharmacological interventions and compared it with the following data points without observing a marked effect. A circadian rhythm of body temperature with 12 h between lowest and peak temperature seems not to be relevant in our study period of 8 h and shorter segments of remounting temperatures.

In contrast to other studies [12, 20, 22], the brain temperature in our evaluation was not consistently higher than in the arterial blood or in the urinary bladder. Nevertheless, monitoring of the brain temperature with thermistors in the ventricular system or in the deep brain parenchyma (at least 2 cm below the cortical surface [13]) is essential to study the effectiveness of new devices for selective cerebral cooling.

Because of the description of the higher temperature in any brain structure than in the rest of the body, as well as the faster and more obvious changes of temperature in the brain [22, 23], there is a necessity to use specific devices to cool especially the brain. An increase in blood temperature would heat the well-perfused brain rapidly, and a decrease in blood temperature would lead to a rapid decrease of the brain temperature, respectively [23]. As shown in other studies selective brain cooling with a cap is not sufficient, for which reason the future selective cooling devices should be restricted to cooling the arterial flow of the neck [13, 15, 24, 25].

The idea to develop new devices for selective neuroprotective cooling of the brain parenchyma has already been published [12, 26–32]. In each of the studies, the device became more specific and smaller [33]. Future improvements of the local cooling system must be performed with the intention to improve the material properties of the neck pads concerning the contact surface and the heat transfer coefficients.

Limitations

Concerning this new neck pad device several limitations have to be discussed. We studied nine consecutive patients

without classifying the neck type in slim, thick, and short necks. The study is limited by only a small number of patients and fever episodes and no control group. No extended monitoring values such as CO_2, detailed changes of heart rate, blood pressure, or respiration were taken into account in this first evaluation study. Having small temperature decreases and continuing standard fever treatment in a small patient group makes it difficult to differentiate between the definitive effect of the neck pads and spontaneous fever curve.

In future studies with an optimized neck pad and a larger number of patients, including a control group, a differentiation between different neck sizes is recommended.

Conclusion

This study showed the practicability of local cooling for intractable fever using the newly developed neck pads in the daily setting of NICU patients.

Representing the first observational study without the use of a control group, it is not possible to determine whether selective cooling of the neck with these pads might be efficient in decreasing intractable fever and sustaining normothermia over a prolonged period.

Acknowledgments The project was supported by the GEBERT-RÜF foundation.

References

1. Badjatia N. Hyperthermia and fever control in brain injury. Crit Care Med. 2009;37:250–7.
2. Mayer SA, Kowalski RG, Presciutti M, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. Crit Care Med. 2004;32:2508–15.
3. Wang CX, Stroink A, Casto JM, Kattner K. Hyperthermia exacerbates ischaemic brain injury. Int J Stroke. 2009;4:274–84.
4. Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology. 2001;56:1299–304.
5. Commichau C, Scarmeas N, Mayer SA. Risk factors for fever in the neurologic intensive care unit. Neurology. 2003;60:837–41.
6. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med. 2004;32:1489–95.
7. Laupland KB. Fever in the critically ill medical patient. Crit Care Med. 2009;37:273–8.
8. Benarroch EE. Thermoregulation: recent concepts and remaining questions. Neurology. 2007;69:1293–7.
9. Morrison SF, Nakamura K, Madden CJ. Central control of thermogenesis in mammals. Exp Physiol. 2008;93:773–97.
10. Wright CL, Burgoon PW, Bishop GA, Boulant JA. Cyclic GMP alters the firing rate and thermosensitivity of hypothalamic neurons. Am J Physiol Regul Integr Comp Physiol. 2008;294:1704–15.
11. Yoshida K, Li X, Cano G, Lazarus M, Saper CB. Parallel preoptic pathways for thermoregulation. J Neurosci. 2009;29:11954–64.
12. Nelson DA, Nunneley SA. Brain temperature and limits on transcranial cooling in humans: quantitative modeling results. Eur J Appl Physiol Occup Physiol. 1998;78:353–9.
13. Keller E, Mudra R, Gugl C, Seule M, Mink S, Frohlich J. Theoretical evaluations of therapeutic systemic and local cerebral hypothermia. J Neurosci Methods. 2009;178:345–9.
14. Zhu L, Diao C. Theoretical simulation of temperature distribution in the brain during mild hypothermia treatment for brain injury. Med Biol Eng Comput. 2001;39:681–7.
15. Bommadevara M, Zhu L. Temperature difference between the body core and arterial blood supplied to the brain during hyperthermia or hypothermia in humans. Biomech Model Mechanobiol. 2002;1:137–49.
16. English MJ, Hemmerling TM. Heat transfer coefficient: Medivance Arctic Sun Temperature Management System vs. water immersion. Eur J Anaesthesiol. 2008;25:531–7.
17. Lerch C, Yonekawa Y, Muroi C, Bjeljac M, Keller E. Specialized neurocritical care, severity grade, and outcome of patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2006;5:85–92.
18. Badjatia N, Strongilis E, Prescutti M, et al. Metabolic benefits of surface counter warming during therapeutic temperature modulation. Crit Care Med. 2009;37:1893–7.
19. Broom M. Physiology of fever. Paediatr Nurs. 2007;19:40–4.
20. Cabanac M. Selective brain cooling and thermoregulatory setpoint. J Basic Clin Physiol Pharmacol. 1998;9:3–13.
21. Biddle C. The neurobiology of the human febrile response. AANA J. 2006;74:145–50.
22. Kiyatkin EA. Brain temperature fluctuations during physiological and pathological conditions. Eur J Appl Physiol. 2007;101:3–17.
23. Brengelmann GL. Specialized brain cooling in humans? FASEB J. 1993;7:1148–52; discussion 1152–3.
24. Sukstanskii AL, Yablonskiy DA. Theoretical limits on brain cooling by external head cooling devices. Eur J Appl Physiol. 2007;101:41–9.
25. Seder DB, Van der Kloot TE. Methods of cooling: practical aspects of therapeutic temperature management. Crit Care Med. 2009;37:211–22.
26. Corrard F. Selective brain cooling. Arch Pediatr. 1999;6:87–92.
27. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation. 2001;51:275–81.
28. Wang H, Olivero W, Lanzino G, et al. Rapid and selective cerebral hypothermia achieved using a cooling helmet. J Neurosurg. 2004;100:272–7.
29. Liu WG, Qiu WS, Zhang Y, Wang WM, Lu F, Yang XF. Effects of selective brain cooling in patients with severe traumatic brain injury: a preliminary study. J Int Med Res. 2006;34:58–64.
30. Qiu W, Shen H, Zhang Y, et al. Noninvasive selective brain cooling by head and neck cooling is protective in severe traumatic brain injury. J Clin Neurosci. 2006;13:995–1000.
31. Storm C, Schefold JC, Kerner T, et al. Prehospital cooling with hypothermia caps (PreCoCa): a feasibility study. Clin Res Cardiol. 2008;97:768–72.
32. Zhu L. Theoretical evaluation of contributions of heat conduction and countercurrent heat exchange in selective brain cooling in humans. Ann Biomed Eng. 2000;28:269–77.
33. Wang Y, Zhu L. Targeted brain hypothermia induced by an interstitial cooling device in human neck: theoretical analyses. Eur J Appl Physiol. 2007;101:31–40.