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Theoretical evaluations of therapeutic systemic and local cerebral hypothermia

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ABSTRACT

Purpose: To simulate cerebral temperature behaviour with hypothermia treatment applying different cooling devices and to find the optimal brain temperature monitoring.
Methods: Models based on hourly temperature values recorded in patients with severe aneurysmal subarachnoid hemorrhage, taking MRI data, thermal conductive properties, metabolism and blood flow into account were applied to different scenarios of hypothermia.
Results: Systemic hypothermia by endovascular cooling leads to an 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. Cooling with neckbands lead to 35.8 °C for dry and 32.8 °C for wet skin in the deep brain.
Conclusions: With head caps temperatures below 36 °C cannot be reached in the deep brain tissue, whereas neckbands, covering the carotid triangles, may lead to hypothermic temperatures in the deep brain tissue. Temperature sensors have to be applied at least 2 cm below the cortical surface to give values representative for deep brain tissue.

1. Introduction

Mild hypothermia, showing numerous neuroprotective effects, may be effective to limit the extent of secondary brain damage (Bernard et al., 2002; Bigelow et al., 1949; Busto et al., 1989; Maher and Hachinski, 1993; Schwab et al., 1998; Thomé et al., 2005). Prolonged systemic hypothermia (SH), however, is associated with severe side effects, thus possibly negate potential benefits (Gasser et al., 2003; Polderman, 2004a,b; Qiu et al., 2006). Noninvasive selective brain cooling may offer the opportunity to achieve the desired effects with minimal side effects.

The aim of the present study was to develop a model to simulate cerebral temperature behaviour during induction of therapeutic hypothermia, to assess the feasibility of local cerebral hypothermia (LH) by using different cooling devices and to find the optimal reference point for brain temperature monitoring.

2. Methods

2.1. Mathematical model

An extended version of the bio-heat equation model by Pennes was used to describe the thermophysiological dynamics during hypothermia (Pennes, 1948).

$$\delta_{ts} \cdot \rho \cdot C \cdot \frac{dT}{dt} + \nabla \cdot (-k \cdot \nabla T) = \rho_b \cdot C_b \cdot \omega_b(T) \cdot (T_b(t) - T) + Q_{met}(T) \quad (1)$$

where δ_{ts} is a time-scaling coefficient, ρ the tissue density, C the tissue specific heat coefficient, k the tissue specific thermal conductivity tensor, ρ_b the density of blood, C_b the blood specific heat coefficient, $\omega_b(T)$ the blood perfusion rate and $T_b(t)$ the arterial blood temperature and $Q_{met}(T)$ the heat source of the natural metabolism. A homogenous temperature distribution within the carotid arteries was assumed.

The equation has been modified in order to take changes in brain temperature into account (Konstas et al., 2007). The modification of the cerebral blood flow (CBF) can be formulated with a baseline perfusion of ω_0, as:

$$\omega_b(T) = \omega_0 \cdot 2.961^{((T-37)\cdot 0.08401)} \quad (2)$$

The temperature-dependence of the metabolism is described to be

$$Q_{met}(T) = Q_0 \cdot 2.961^{((T-37)\cdot 0.08401)} \quad (3)$$

In order to implement the mathematical equation representing the thermal behaviour of the different tissues finite element based physical models for the head and neck, connected via the blood flow are developed. The mathematical model was implemented using

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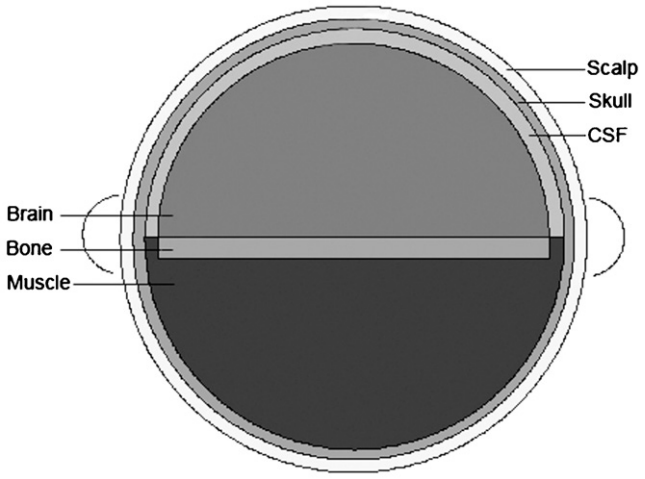

Fig. 1. Coronar section of the head model, including the different tissue types scalp, skull, cerebrospinal fluid (CSF), brain, bone and muscle.

the commercial software package COMSOL based on the Finite Element (FE) method. The specific heat constants are taken from the literature for blood (Dexter and Hinderman, 1994), scalp, skull, muscle and brain (Xu et al., 1999), cartilage (Karam et al., 2006), as well as constants for the mass density and thermal conductivity for blood, scalp, skull, muscle and brain (Olsen et al., 1985) and cartilage (Karam et al., 2006). The values for the cerebrospinal fluid are supposed to be equal to those from water.

In order to implement the mathematical equation representing the thermal behaviour of the different tissues finite element based physical models for the head and neck, connected via the blood flow are developed.

2.2. Physical models

2.2.1. Physical model of the head

The three-dimensional head structure is approximated as a spherical model (Fig. 1) Diao et al., 2003; Zhu and Diao, 2001). The brain tissue is surrounded by a layer of cerebrospinal fluid (CSF). The lower half of the sphere represents the facial structures and is modelled as muscle tissue. The two halves are separated by a bone plat, representing the skull base. Two outer layers, a skull- and a scalp-layer, surround the complete sphere. Based on anatomical data the outer radius of the brain tissue layer is set to have a radius of r_{Brain} = 80 mm resulting in a brain volume of 1080 ml. The CSF layer in the upper half of the sphere is set with r_{CSF} = 85 mm. The thickness of the skull is chosen to be 5 mm, implying that the outside radius of the skull layer is r_{Skull} = 90 mm. The thickness of the scalp-layer is also chosen to be 5 mm resulting in an outer radius of the head model of 95 mm.

2.2.2. Physical model of the neck

The neck model is based on a axial T1 weighted fast field echo MRI scan of a healthy volunteer (3T, Phillips Achieva). The cross section is placed at the level of the carotid bifurcation. The segmentation within the cross section allowed for the differentiation of bone, skin, muscle and throat within the neck. The diameters of the skin, spine, trachea and larynx have been measured and implemented in the neck model. The position of arteries and veins within the cross section were determined. The mapped cross section of the neck was extruded to a 10 cm long three-dimensional structure.

2.3. Evaluated scenarios

The models described are applied for different scenarios to analyze different cooling methods, defined by setting the boundary conditions between the cooling device and the skin layer to be 6 °C.

2.3.1. Systemic hypothermia

For the scenario of SH, cooling via the decreased systemic blood temperature is simulated. The model is based on hourly temperature values recorded in nine patients with severe aneurysmal subarachnoid hemorrhage, treated with SH due to elevated intracranial pressure (ICP) and/or symptomatic cerebral vasospasm refractory to conventional treatment (Gasser et al., 2003). SH was induced and maintained with an intravascular catheter-based heat exchange system (Alsius, Irvine, CA) and hourly temperature values were collected for the brain with temperature sensors integrated in ventricular drainages (Raumedic, Munich, Germany) and for the body core with sensors in the femoral artery (Picco System, Pulsion Medical System, Munich, Germany).

2.3.2. Local cerebral hypothermia with a cooling cap applied over the skull

For the scenario of LH, cooling via a boundary condition of 6 °C, set at the upper half of the sphere, representing the skullcap is simulated. The heat transfer from the scalp to the head cap device is described by the heat flux condition:

$$-\vec{n}(-k\nabla T) = h(T_{inf} - T)$$

The heat transfer coefficient was estimated for dry skin to be h_{dry} = 8.37 W/(m^{2}K) and for wet skin h_{wet} = 29.3 W/(m^2 K) (De Dear et al., 1997).

2.3.3. Local cerebral hypothermia with a neckband

An alternative approach for LH is analyzed to lower the temperature within the arterial blood supply in the carotid arteries leading to the head. A neckband is simulated to be placed around the neck. The head and neck model are linked via the heat exchange of the blood flow between neck and head.

The external cooling of the neck causes a temperature decay within the neck tissue, which is used to model the temperature of the blood supply to the brain. The heat flux of the arterial blood coming from the cooled neck is transposed into a blood perfusion rate for the brain tissue. The metabolic rate of the brain tissue is set in dependence of the blood temperature as earlier described in the first test scenario within Eq. (2).

3. Results

SH by endovascular cooling leads to an almost uniform temperature decrease within the brain tissue over time (Fig. 2). On the other hand, cooling with head caps applied over the scalp leads to a temperature of 33 °C only in the superficial brain layers (Fig. 3). After 6 h the scalp reaches a temperature of 15 °C, the brain surface 33 °C, while the deep brain tissue still remains on a temperature higher than 36 °C.

Cooling with a neckband leads to a temperature decay limited to the outside layers of the neck (Fig. 4). Only the blood supply, however, leading to the brain within the carotid arteries is relevant for LH of the brain. The relevant region, the region of the carotid triangle, can be cooled with cooling elements covering only the frontal part of the neck, as shown in Fig. 4. In all three scenarios (Fig. 4a–c) a temperature drop appears from 37 °C to ≤35.5 °C in the carotid arteries within 3 h of cooling. The cooling of the muscles in the dorsal regions of the neck has no influence. In Fig. 5 the differences in the temperature decrease due to the different heat transfer coeffi-

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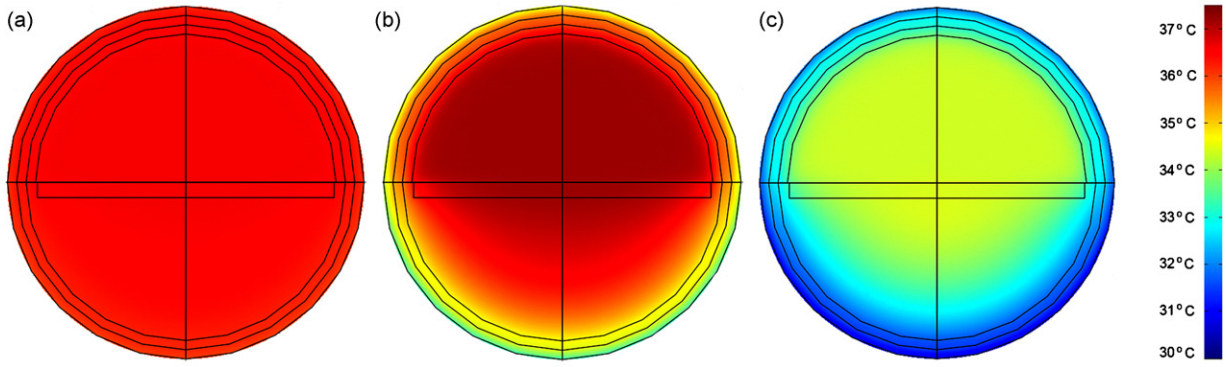

Fig. 2. Coronar section of the head model giving the temperature values in the different tissues and the brain. The temperature decay within the layered head model is shown for systemic hypothermia (SH) for (a) 10 min; (b) 1 h; and (c) 6 h of cooling. SH by endovascular cooling leads to an almost uniform temperature decrease within brain tissue.

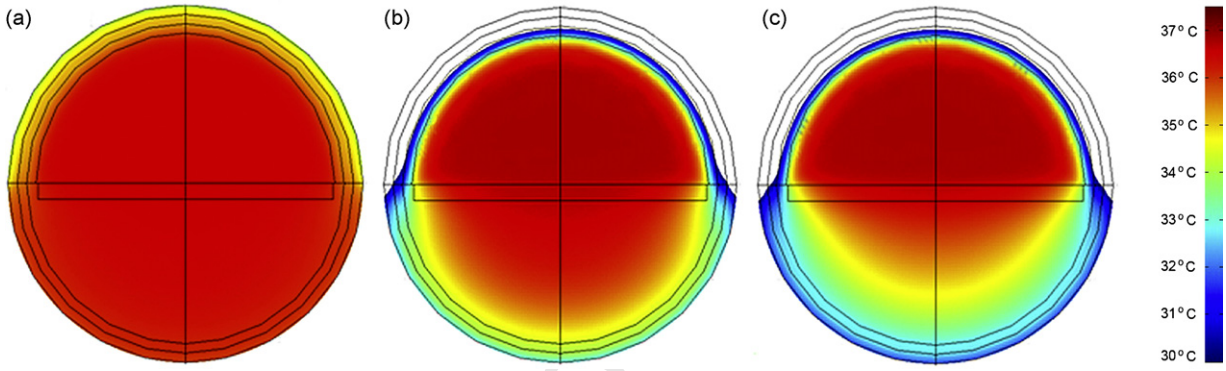

Fig. 3. Coronar section of the head model giving the temperature values in the different tissues and the brain. The temperature decay within the layered head model is shown for local cooling with a head cap for (a) 10 min; (b) 1 h; and (c) 6 h of cooling. After 1 h the skin layer has reached a temperature below 20 °C (white colour in the figures), while the deep brain tissue remains unaffected.

cients for dry and wet skin are shown for cooling after 6 h within the axial section of the neck. Already after 3 h the temperature of the tissue surrounding the carotid arteries have reached a temperature of 32 °C. Cooling using the neckband leads to brain temperatures of 35.8 °C for dry skin and 32.8 °C for wet skin (Fig. 6).

The brain temperature decay was calculated over time for cooling with the head cap with reference points chosen in 5 mm steps starting at the skin surface and leading into the brain tissue. In a depth of 2 cm below the brain surface no temperature change can be observed. A temperature sensor has to be placed at least 2 cm below the brain surface to monitor the temperature values representative for deep brain tissue.

4. Discussion

Our theoretical studies indicate that cooling with head cap over the scalp alone leads to a temperature of 33 °C only in the superficial brain layers, while the deep brain tissue still remains on a temperature higher than of 36 °C. These results are in agreement with simulations performed by Nelson and Nunneley, as well as by Zhu and Diao (Nelson and Nunneley, 1998; Zhu and Diao, 2001). Recent theoretical approaches suggest that a decrease in the human brain temperature can be accomplished only due to a temperature decrease in the incoming arterial blood flow (Sukstanskii and Yablonskiy, 2007). A temperature shielding effect of the CBF has

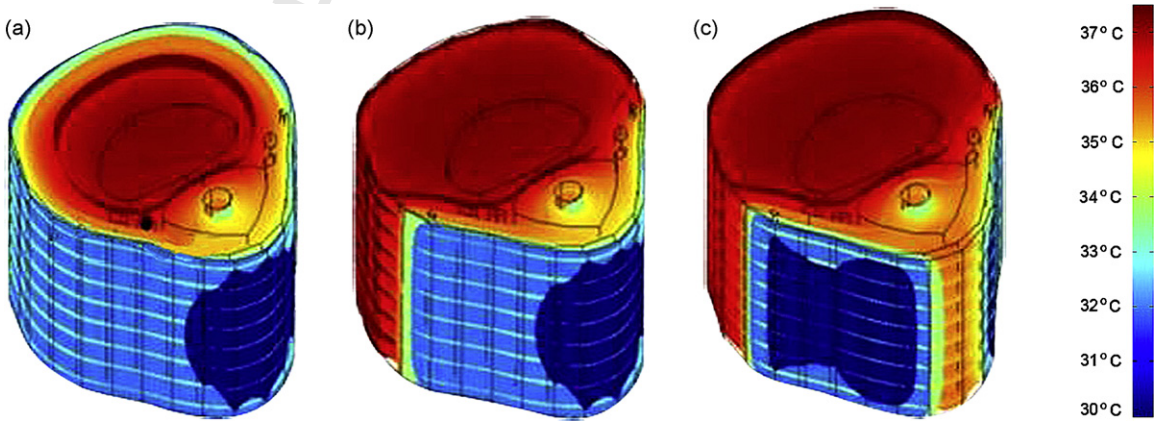

Fig. 4. 3D views of the neck model giving the temperature values for (a) cooling for 6 h with a cold neckband surrounding the whole neck; (b) cooling for 6 h with the cooling parts of the neckband at the anterior part of the neck; and (c) cooling for 6 h with the cooling parts of the neckband at the carotid triangles of the neck.

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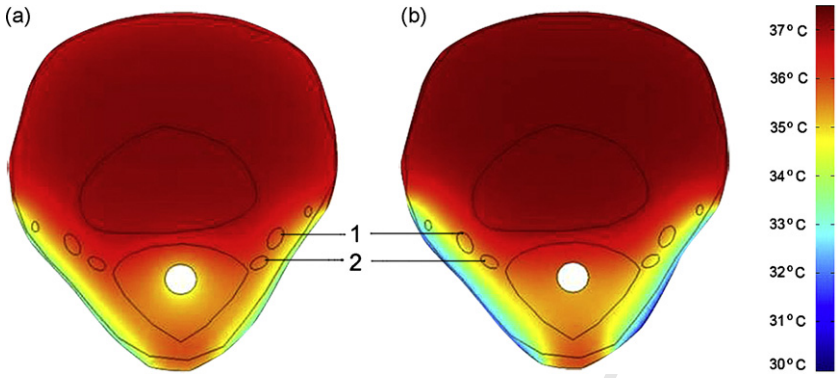

Fig. 5. The axial section of the neck model with temperature values is shown for cooling for 6 h with the neckband at the carotid triangles of the neck (a) with a heat transfer coefficient for dry skin and (b) with a heat transfer coefficient for wet skin. (1) Internal jugular vein; (2) internal carotid artery.

been described (Sukstanskii and Yablonskiy, 2007; Zhu and Diao, 2001; Zhu et al., 2006). CBF counteracts extracranial cooling and prevents the deep brain tissue from temperature decrease (Diao et al., 2003; Sukstanskii and Yablonskiy, 2007; Zhu et al., 2006). Sukstanskii et al. suggested that only under the condition of very low CBF (6 ml/100 g/min) and an ideal heat transfer coefficient describing the heat exchange between the head surface and a cooling helmet would allow a temperature decrease within deep brain tissue (Sukstanskii and Yablonskiy, 2007). Wang et al. supported these theoretical considerations with a case report (Wang et al., 2006). A patient with left carotid internal artery occlusion was treated with LH. The authors found, with bilateral intraparenchymatous ICP- and temperature-monitoring, significant interhemispheric ICP- and temperature-gradients with preferential cooling of the infarcted, low-perfused hemisphere. Wang et al., applying a specifically developed cooling device for external head cooling and a temperature monitoring probe 0.8 cm below the cortical surface, showed in a first study group of 8 patients, that after a mean of 3.4 h, a brain temperature lower than 34 °C could be reached (Wang et al., 2004). In another patient series, ICP-lowering effects in 45 patients with severe traumatic brain injury could be achieved with a similar cooling device for external head cooling (Qiu et al., 2006). With a temperature monitoring probe introduced 10 mm below the brain surface or into the space where the intracerebral haematoma had been evacuated, the authors documented a brain temperature decrease to 33–35 °C within 2 h (Qiu et al., 2006). However, in both studies performed by Wang et al. and by Qiu et al., not only a head cap, but a neckband was integrated and applied simultaneously (Qiu et al., 2006; Wang et al., 2004; Wang et al., 2006). Based on our results, only the neckband, effective in cooling the blood inflow within the carotid arteries may have contributed to the desired effect of LH in these studies. With future developments in cooling devices for LH it should be taken into account that only the neckband may be effective to accomplish LH in the deep brain tissue. The further development of head caps, not only being useless, but potentially harmful concerning wound healing especially in neurosurgical patients should be abandoned.

Animal and clinical trials showed that even small changes in brain temperature can determine the survival of cerebral tissues during ischemia (Azzimondi et al., 1995; Busto et al., 1989). Fever has been shown to be harmful in patients with brain damage and interests increase for a valuable brain temperature monitoring in neurointensive care patients (Azzimondi et al., 1995; Diringer, 2004; Oliveira-Filho et al., 2001). In clinical studies applying LH, temperature monitoring is not standardized (Hachimi-Idrissi et al., 2001; Liu et al., 2006). Under pathological conditions, the temperature of the brain tissue are insufficiently represented by the trunk core or the tympanic temperature (Mariak, 2002; Mellergard and Nordström, 1990). Our results suggest, that the ideal reference point for temperature monitoring to control the success of LH is at least 2 cm below the cortical surface. Based on our simulations, surface cooling by a head cap induces a temperature gradient in the brain tissue of 3 °C for the first 1 cm. Zhu and Diao, in their model simulations found, depending on the head surface temperature, a temperature gradient of up to 13 °C in the brain tissue (Zhu and Diao, 2001). This implies that the results of Wang et al. with a temperature sensor applied to a probe at 0.8 cm below the cortical surface are not representative for the deep brain tissue (Wang et al., 2004; Wang et al., 2006). Their approach for temper-

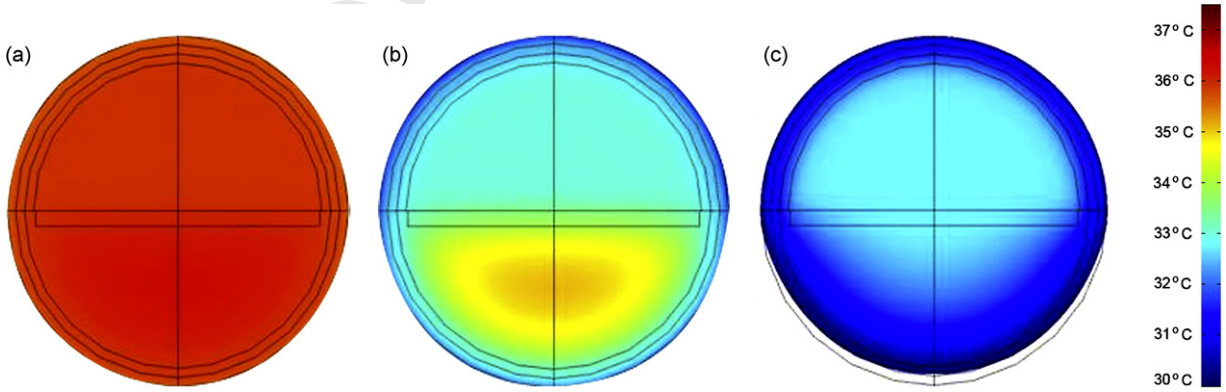

Fig. 6. The coronar section of the head model giving the temperature values in the different tissues and the brain. The temperature decay within the layered head model is shown for local hypothermia with a neckband and wet skin after (a) 10 min; (b) 1 h; and (c) 6 h.

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ature monitoring is based on theoretical examinations from Zhu and Diao, suggesting that the volumetric-averaged brain temperature should be measured at 7.5 mm below the cortical surface (Zhu and Diao, 2001). The debatable question remains, which brain temperature values are representative to control the effects of LH: the volumetric-averaged brain temperature taken from Zhu and Wang or the temperature coming centripetal from the cortical surface to the deeper brain, where no change can be observed anymore and reflecting the temperature in the deep brain. The hypothesis from Zhu and Diao, that the volumetric-averaged brain tissue temperature may be associated with patient outcomes lacks some pathophysiological considerations. Especially applying therapeutic hypothermia after cardiac arrest, leading to global changes and mitigating neurologic injury in the whole brain (Bernard et al., 2002; Safar and Kochanek, 2002), suggests, that the temperatures should be monitored and hypothermic values aimed not only in the distal, but in all regions of the brain. Histological damages with death of neurons were documented mainly in the most vulnerable regions of the brain, such as the hippocampus and the cerebellum (Safar, 1997).

Transferring the results from our model simulations into clinical practice, several limitations have to be discussed. Spontaneous temperature variations within the brain occur under physiological and pathological conditions (Baker, 1982; Mellergard and Nordström, 1990). Local CBF, cerebral metabolism and the temperature of the perfusing arterial blood, supposed to be constant in our model, may be altered globally in the whole brain, e.g. with fever or hypothermia, or focally, e.g. with ischemic stroke (Keller et al., 2000). The cerebral metabolic rate, most of all, may be variable. With treatment of fever, counterregulation may occur, which partially could be blocked medically. Furthermore, effective cooling of the head and brain may lead to a secondary cooling of the entire body. These conditions may change during the illness course and treatment (Hegner et al., 2001). These phenomenon lead to still more complex conditions for brain temperature monitoring and model simulations. In future, theoretical examinations have to be individualized not only focusing the influence of different cooling devices, but adapted specifically to the specific pathophysiological conditions of the patients.

In conclusions: The model simulations indicate that SH with a intravascular catheter-based heat exchange system leads to a uniform temperature decrease within the brain. With cooling head caps, attached over the scalp, temperatures below 36 °C cannot be reached in the deep brain tissue, whereas a neckband, covering the carotid triangles, via a temperature decrease in the blood flow to the brain may lead to hypothermic temperatures in the deep brain tissue. Cooling via a neckband (boundary conditions of wet skin, 6 °C) leads to a temperature of the deep brain of 32.8 °C within 6 h. In future clinical studies, the temperature monitoring should be standardized. Temperature sensors, applied at least 2 cm below the cortical surface represent values from deep brain tissue.

Q4 Uncited references

Serota (1939), Severinghaus (1962), Simon (2007) and Sukstanskii and Yablonskiy (2004).

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