In the present study, 54% of the PIDs in the hypothermic rats enlarged the high-intensity area of fluorescence, similar to that seen in normothermia (53%). In addition, we found that the area enlarged by each PID was significantly larger in hypothermia than in normothermia. Since the increase in NADH fluorescence indicates disproportion in oxygen balance [11] and correlates with low ATP and high lactate levels [18], and since the cortex corresponding to the enlarged area showed infarction 24 h after the onset of ischemia in the present study, we suggest that PIDs in hypothermia contribute to the increase in infarct volume more than those in normothermia and that therapies designed to prevent the development of PIDs in the presence of hypothermia might be important in any treatment strategy designed for stroke. This conclusion is supported by the results of a study by Ikonomidou et al. [10] demonstrating that hypothermia combined with MK-801, an NMDA antagonist, is more effective against hypoxic/ischemic brain damage than hypothermia or MK-801 alone.

NADH fluorescence images showed that hypothermia delayed the initiation of the first and second PIDs. Since PIDs can be suppressed by administration of glutamate antagonists [9,13] and since PIDs are initiated at the edge of the ischemic core, the increase in glutamate in the margin of the ischemic core is considered to be related to the mechanism of initiation of PIDs. Baker et al. [2] found that hypothermia delayed the increase in glutamate tissue concentration in the ischemic core. Thus, it is possible that the delay in increase in glutamate in the ischemic core during hypothermia is due to a delay in the initiation of PIDs.

In conclusion, we elucidated the effects of hypothermia on the manner of propagation of PIDs with temporal and spatial resolutions by using NADH fluorescence images. Although hypothermia delayed the appearance of PIDs, it did not suppress the occurrence of PIDs. Therefore, we suggest that the lack of hypothermic protection against permanent focal ischemia contributed to the lack of reduction in PID generation. The high-intensity area of NADH fluorescence that was enlarged by each PID was larger in hypothermia than in normothermia. These results suggest that PIDs in hypothermia could have a greater effect on growth of infarction than those in normothermia. These findings emphasize the importance of therapies designed to suppress PIDs even during hypothermia in the acute stage of focal ischemia.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2008.10.054.

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Heat Transfer Characteristics of a Pharyngeal Cooling Cuff for the Treatment of Brain Hypothermia[*]

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Abstract

In the present study, the characteristics of both flow and heat transfer in a pharyngeal cooling cuff for the treatment of brain hypothermia were investigated experimentally and numerically. The pharyngeal cooling cuff, which is a balloon-like structure placed in the pharynx, was developed for medical purposes. As a method for controlling the brain temperature, cooling water, which is physiological saline at 5°C, is injected into the cuff in order to cool the common carotid artery, which is adjacent to the pharynx. In this study, the heat transfer characteristics between the cuff wall and phantom body, which was considered to be equivalent to the human body, were experimentally determined, and the flow behaviour in the cuff was observed in detail. Furthermore, a three-dimensional numerical simulation was carried out to investigate both the flow velocity and temperature distribution in the cuff.

Key words: Pharyngeal Cooling, Brain Hypothermia, Medical Engineering, Numerical Simulation, Heat Transfer

1. Introduction

In Japan, cerebropathy, including cerebrovascular disorder, is one of the causes of death following malignant neoplasms and heart diseases(1). Crisis prediction in the case of cerebrovascular disorders and elucidation of the mechanism underlying the development of these disorders are the need of the day. Further, the establishment of a good method for treating the recurrence of neurological condition, including the society return, is strongly desired. Hayashi(2)~(3) revealed that one of the therapies for lowering the brain temperature in the case of serious wound injuries to the head, severe cerebrovascular disorders, or brain ischemia was cardiopulmonary stop; Patients treated with this method were found to have a good neurological prognosis(4)~(5). At present, low-temperature brain therapy enables the controls of the brain temperature and intracranial pressure in the case of patients with severe brain damage who satisfy the condition variously. This therapy has been introduced to repair nerve cells damaged during the initial brain damage, and to prevent the development of secondary brain damage. Since the release of neurotransmitters and action of free radicals are both drastically suppressed at brain temperatures of 32°C or less, it is said that

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the brain is protected against damage. For the purpose of treatment, brain hypothermia is divided into mild hypothermia (core temperature, 34°C) and moderate hypothermia (32°C). The temperature of the brain is lowered and maintained at low temperatures by lowering the body temperature. The latter is achieved by covering the whole body with a water-cooled blanket. In this method, the patient's body is wrapped with a water-cooled blanket, and cold water (approximately 20°C) is circulated through the blanket. It is also possible to simultaneously maintain the brain temperature at the desired degree and strictly monitor the temperature. However, this management strategy, i.e., conventional hypothermia treatment, requires a great deal of time to bring about changes in body temperature and for acute state transition of the pathology. Therefore, research and development on medical instruments such as water-cooling blankets, headgear, and mufflers for the purpose of cooling of body parts and lowering the brain temperature are widely being conducted(6).

Takeda et al.(7)~(8) developed the pharyngeal cooling cuff by analyzing the anatomy of the pharynx division. This cuff is inserted through the oral cavity of the patient, and it can cool the common carotid artery, which is located approximately 10 mm outside the pharynx division. Thus, cooling and temperature control of the brain is possible via the cooling of the main blood vessel that supplies the brain. In comparison with conventional whole-body cooling, the pharyngeal cuff method rapidly lowers the brain temperature. Moreover, the countermeasures of acute brain temperature management and early brain cooling during life-threatening emergencies related to brain diseases are possible with the latter method. For acute phase of brain cooling, we assume that physiological saline at 5°C should be used to cool the cuff. During animal testing(9), this cuff has been shown to produce a good cooling effect on the brain. However, the optimum cooling efficiency of this cuff has not been determined since the structure of this device is based on the pharynx shape.

On the basis of this background, we aimed to understand the flow and heat transfer characteristics of the pharyngeal cooling cuff. In this report, in order to evaluate pharyngeal cooling, we analyzed the heat transfer between the cuff and a phantom body (hereafter referred to as phantom), which was considered to be equivalent to the human body. In particular, we focused on the thermal transport characteristics within the cuff. Further, computational fluid dynamics (CFD) analysis was carried out to analyze the flow in the cuff, and the cooling efficiency was examined under various conditions. These results are useful as they provide the basic information required to develop the clinical applications of the cuff and to improve the cuff to ensure better cooling of the pharynx. Future studies will address transport within the surrounding tissue and the effectiveness of carotid artery blood cooling.

Nomenclature

D : Diameter
L : Length
Q : Heat quantity
q : Heat flux
S : Surface area
T : Temperature
⊿T : Temperature difference t
U : Velocity
V : Inlet flow
X : Local position
η : Cooling efficiency
ρ : Density

Subscript
1~6 : Thermocouple
in : Inflow
L : Liquid phase
out : Outflow
Pha : Phantom

2. Experimental setup and procedures

2.1. Pharyngeal cooling cuff

The structure of the pharyngeal cooling cuff and a schematic diagram of the working of the cooling cuff are shown in Figures 1 and 2, respectively. In the case of patients with difficulties in voluntary respiration, the pharyngeal cooling cuff is inserted into the pharynx division along with the tube for artificial respiration. Therefore, the shape of the cuff is based on the shape of the pharynx division. The upper and lower parts of the cuff are placed in the pharynx and upper esophageal divisions, respectively. The cooling cuff, which is a balloon-like structure, is 0.5 mm in thickness and made of polyvinyl. It is 250 mm long with a total volume of 100 ml. The cooling cuff has an inlet tube and 2 outlet tubes, which are 4 mm in diameter. The basic flow behavior within the cooling cuff is as follows. Cooling water, which is physiological saline at around 5°C, flows into the inlet tube. The cooling water passes through the cuff and reaches the tip of the cuff. At the tip, the inlet

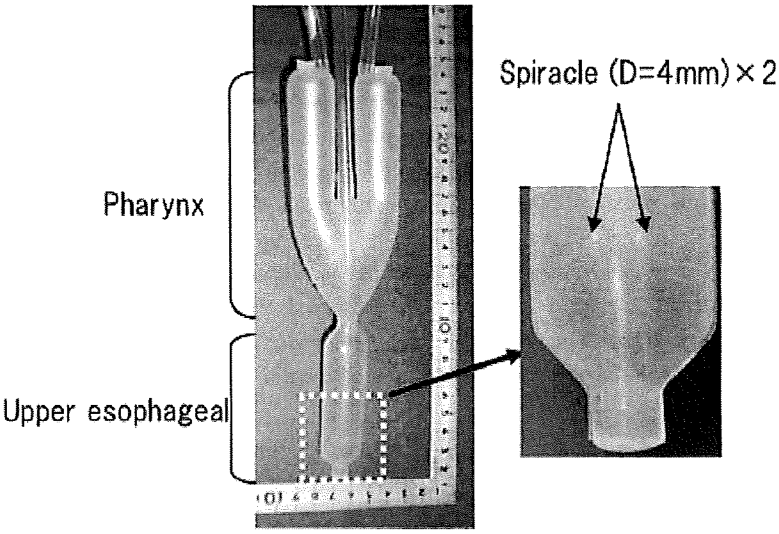


Figure 1 Appearance of pharyngeal cooling cuff

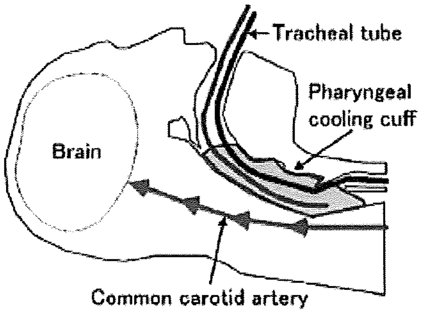


Figure 2 Image of the pharyngeal cooling cuff for brain hypothermia treatment

tube has 2 spiracles, 4 mm in diameter, on the tube wall. After passing through the spiracles, the cooling water, which is between the cuff and inlet tube, flows to the upper part of the cuff. During this time, the cuff wall is cooled by heat transfer between the inner cuff wall and the cooling water. Finally, in the upper part of the cuff, the cooling water flows in 2 directions and out through the outlet tubes.

2.2. Experimental apparatus and procedures

A schematic diagram of the experimental facility used in the present investigation is shown in Figure 3. The experimental apparatus includes a heater; a cooling water circulatory system, including a flow-control device; measuring equipment; and the cuff that is placed in the phantom. The cooling water circulation apparatus can adjust the temperature and quantity of cooling water flowing into the cuff. Distilled water was used as the working fluid. The running water temperature was measured with a K-type thermocouple (D = 0.3 mm) inserted into each tube. The phantom can be maintained at temperatures ranging from room temperature to 45°C, by adjusting the heater. The K-type thermocouple (D = 0.3 mm) was positioned in the phantom at 6 points (T_1 ~ T_6; positions are shown in Figure 7) between 2 places, cuff and phantom, and the phantom temperature and local surface temperature of the cuff were measured. All thermal data were fed into computers through a data logger at 1s intervals.

The phantom was maintained at the setting temperature, after the specified quantity of cold water at the desired temperature was passed through the cuff, while the output of the band heater, which was wound around the phantom circumference, was adjusted by heat transfer. In the temperature setting of the phantom, the mean values of the 2 thermocouples installed near the cuff were adjusted to the phantom temperature. The data were collected, after a steady state was achieved.

For the visualization experiment, the cuff was placed in the standing position after it was taken out of the phantom, and the observations were made. The water was mixed with insoluble fluorescent particles ($d = 165$ μm, $\rho = 1050$ kg/m^3; to trace the water dispersion) for better visualization. A specified quantity of this water was supplied, and the flow behavior was recorded with a digital video camera.

The inflow temperature ranged from $T_L = 3$~10°C during the experimental conditions, and the inflow, V = 100~1500 ml /min. The temperature of the phantom was maintained at

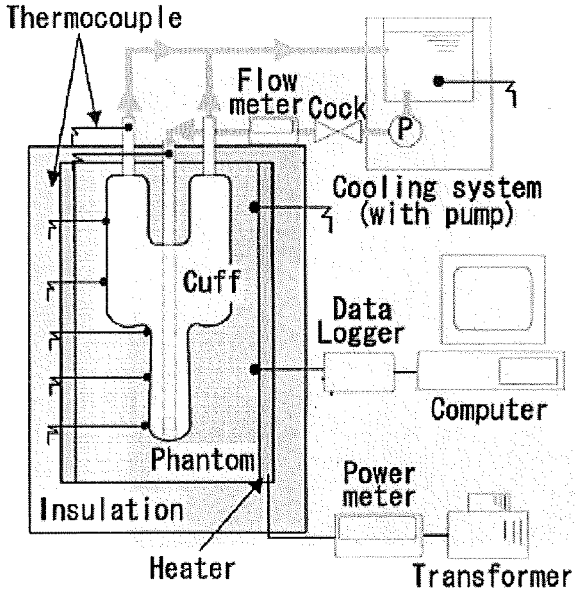


Figure 3 Experimental apparatus

T_{Pha} = 35~38°C. In addition, the measurement accuracy of this experiment was as follows. The relative temperature difference of the thermocouple was within 0.4 K. The temperature reading error was within ±2.5%, considering the accuracy of the measuring equipment. The erratic readings of the inflow were within ±0.02% of the accuracy of the flow meter.

2.3. Human body equivalent phantom

The phantom used in this experiment was a wet type one constructed with agar, boric acid, and water. The mould was removed, and the phantom was left to solidify and form a cylindrical vessel. This vessel was used for the experiment and placed in an independent (standing) position. The proportion of the components used to construct of the phantom is shown in Table 1. Furthermore, the thermal conductivity of the phantom measured by the unsteady probe technique as well as the thermal conductivity of the representative organism is shown in Table 2(10). In the experiment, the phantom was lap coated to prevent changes in the water content due to evaporation from the exterior.

Table 1 Principal components of the phantom body

Component	Agar	Boric acid	Water
Ratio (wt%)	3.0	1.2	95.8

Table 2 Thermal conductivity

	Phantom	Ref. (10)
Thermal conductivity (W/(mK))	0.532	0.34~0.68

2.3. Calculation grid and numerical analysis method.

The GAMBIT grid generation software was used for analysis of three-dimensional CAD data from the cuff to prepare a calculation grid. The calculation grid comprised a triangular 8-faced cone grid in the cuff interior and in the vicinity of the wall. The calculation grid is shown in Figure 4 (left: coronal plane, right: median section). The calculation grid number of the cuff is shown in Table 3. In the numerical analysis, the thermo-hydrodynamic analysis software FLUENT was used.

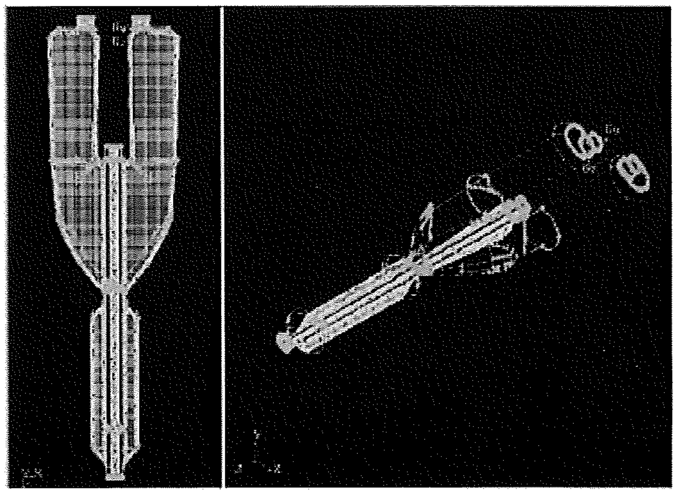


Figure 4 Numerical grid for the cuff (3D)

Table 3 Grid size of the cuff model

Cells	Faces	Nodes
803,759	1,805,366	261,420

3. Results and Discussion

3.1. Surface temperature of cuff

The relationship between surface temperature and inflow at different positions in the cuff is shown in Figure 5. The phantom temperature and inflow temperature were fixed at 37°C and 5°C, respectively. The horizontal axis of the figure indicates the thermometry position of the cuff. When the inflow is small, the cuff surface temperature is generally higher. Furthermore, no large differences in the inflow temperature were observed at the different cuff positions. However, the surface temperatures at positions 3, 5 and 6 were lower than the temperature at the other positions in the cuff. Due to these reasons, another factor was considered. At around position 3, there was an increase in the flow velocity with a rapid decrease in the water course at the cross section of the cuff center, which led to an increase in the heat transfer coefficient, thereby enhancing the cooling effect. Furthermore, near position 5, after the fluid that passed through the center of the cuff was pooled in the bifurcation, this fluid was divided between both the cuff branches; the water pools again, and the local heat transfer increases. Thus, there is increased heat transfer at position 6 due to this complicated flow, including the rotational flow, generated near the cuff exit.

3.2. Heat transfer characteristic from cuff surface

Complicated flow, including rotational flow, through the cuff facilitates heat transfer to a large extent within the cuff surface. The purpose of the cuff is to cool the biotissue in the pharynx division. Therefore, it is important to understand the heat transfer characteristics between the cooling water and cuff wall surface through which the water flows. Next, the cooling water inflow (V) and amount of heat transfer (Q) calculated from the temperature gradient (⊿T) were examined. The relationship between the cooling water inflow and

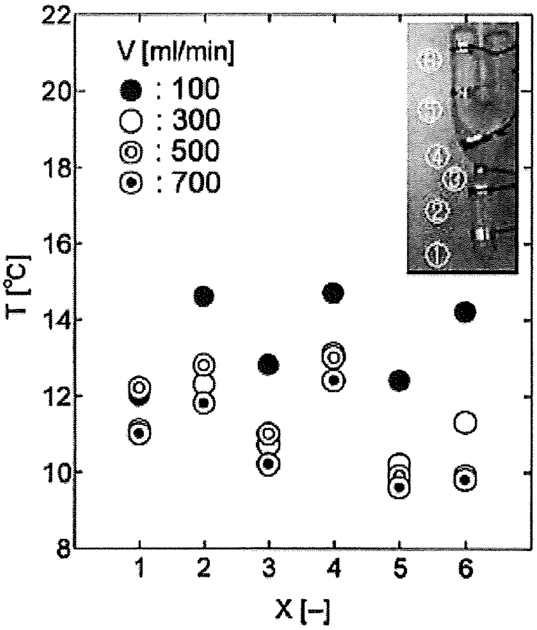


Figure 5 Temperature distribution in the cuff within the phantom

amount of heat transfer and cooling efficiency (η) of the cuff is shown in Figure 6. The cooling efficiency is calculated with the following equations.

$$\eta = \frac{T_{out} - T_{in}}{T_{Pha} - T_{in}} \times 100 \qquad [\%] \qquad (1)$$

Where, T_{in}, T_{out}, and T_{Pha} are the cuff inlet temperature, outlet temperature, and phantom temperature, respectively. The phantom temperature and inflow temperature were fixed at T_{Pha} = 37°C and T_{in} = 5°C. Since the sensible heat traffic volume increases, as the inflow increases, there is a synchronous increase in the amount of heat transfer. In addition, the rapid flow, including the rotational flow, generated in the cuff due to the increased inflow is considered to be a factor inducing an increase in the amount of heat transfer. Moreover, it has been proven that the cooling efficiency exponentially decreases with an increase in the inflow. This is because the increasing temperature gradient (⊿T) of the inflow decreases with increase in the inflow. In particular, the cooling efficiency stabilizes at approximately 6% at an inflow of over 750 ml/min.

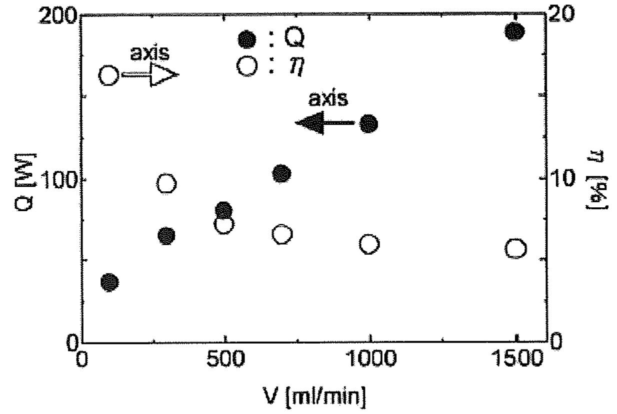
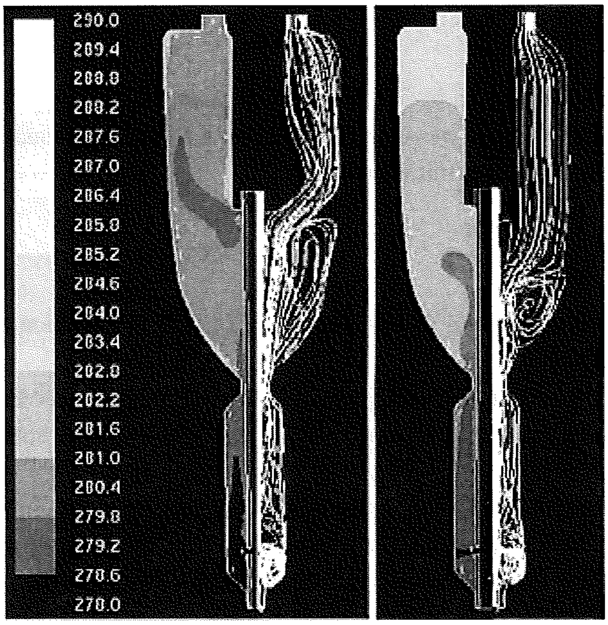


Figure 6 Relation between heat quantity and cooling efficiency

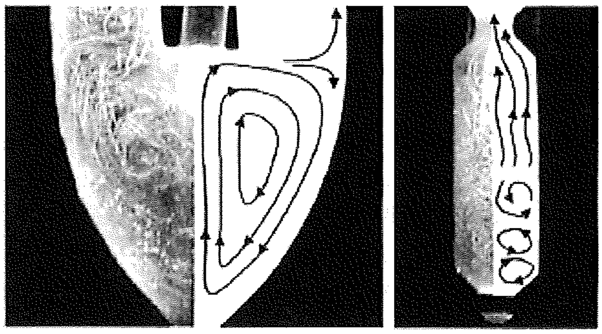
3.3. Flow characteristics in cuff

Numerical results of temperature distribution (left side) and cuff flow pattern (right side) are shown in Figure 7. (a) and (b), respectively, in the case of cooling water inflows of 500 ml/min and 150 ml/min. The inflow temperature was T_{in} = 5°C in both cases. The temperature conditions of the cuff surface during the analysis have been set as follows. On the basis of the relationship between heat quantity and cooling efficiency in Figure 6, in the boundary condition, the heat flux (q), which was divided by the cuff surface area (S = 0.021mm), was calculated in terms of the amount of heat transferred (Q). The heat flux (q) at V = 500 ml/min and 150 ml/min were 3810 W/m^2 and 2068 W/m^2, respectively. The temperature distribution in the cross section of the cuff is shown in Figure 7. In the right figure, the three-dimensional locus of the representative particles is shown in order to demonstrate the flow characteristics in the cuff in terms of the fluid particles. On the basis of the temperature distribution, we observe that the temperature at the tip and in the central section of the cuff is low. In addition, the temperature at the point whereof the fluid pools, i.e., in the area of the rotational flow, is also low. These results are in agreement with the measurement results in Figure 5. Furthermore, the temperature in the cuff in general decreases with the increase in the inflow, and there is insufficient heat exchange. Moreover, as seen in the flow pattern in Figure 8, the fluid in the cuff exhibits a rotational flow in the cuff tip, and it turns at the upper part of the cuff. It was confirmed that there is paired rotational flow at the cuff center for right and left. These flow patterns are largely affected by the change in the inflow. As shown in Figure 7, it is understood that the flow at the cuff central part is runoff without reaching the cuff surface by the rotational flow. This means that the cooling water which has been flowing from below the cuff did not contribute to the heat transfer with the cuff surface. Moreover, it is proved that the central part of the rotational flow is the stagnation point. From these points of view, it seems to be possible that the thermal efficiency increases by suppressing the rotational flow in the cuff. The images in Figure 8 (a) and (b) show the streamlined flow in each part of the cuff. Figure 8 (a) shows the central portion of the cuff and (b) shows the cuff tip. The total inflow is 300 ml/min. Figure 8 (a) shows the paired rotational flow for the right and left after the fluid pooled in the cuff bifurcation and after it was distributed in the arms. After the intense rotational flow in the cuff tip, the fluid turns centrally and flows in a rectilinear manner (Figure 8 (b)). The flow characteristics are in accordance with the numerical result shown in Figure 7.



(a) V=500ml/min (b) V=150ml/min

Figure 7 Numerical results of temperature distribution and flow patterns



(a) Middle part (b) Apical part

Figure 8 Results of the visualization experiment

4. Conclusion

The use of the pharyngeal cooling cuff for the treatment of brain hypothermia was experimentally and numerically analyzed, and this analysis led to the following conclusions.

(1) It was possible to clarify the heat- transfer characteristics of the pharyngeal cooling cuff experimentally and numeric-analytic. Furthermore, the results of this simulation result agreed with the experimental results.

(2) The cooling efficiency and amount of heat transfer in the cuff are dependent on the inflow. However, it is considered that heat transport efficiency and local heat exchange lower by the rotational flow in the cuff. The cooling efficiency stabilizes at 6%, when the inflow is greater than 750 ml/min. This is a very low value, and further improvements in the cuff are necessary. Currently we are performing both experimental and computational analysis on a cuff design which suppresses the rotational flow structure.

Acknowledgements

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専門医に求められる
最新の知識 Neuroscience

脳神経外科速報 vol.19 no.2 185～192, 2009

脳低温療法の基礎

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脳低温療法は非特異的に代謝経路を抑制し治療効果を発揮している．成人の心停止蘇生後脳症や新生児の低酸素性虚血性脳症に対する臨床研究では，脳低温療法は良好な結果を示している．頭部外傷後の脳低温療法や，破裂性脳動脈瘤のクリッピング手術における術中脳低温療法では，否定的な結果が報告され，適応を考慮する必要がある．脳梗塞に対しては大規模臨床研究は行われていない．ジェルパッドによる体表冷却や，血管内冷却カテーテルによる血液冷却は，体温の低下が比較的早く，目標温に達した後の温度のコントロール性にも優れている．鼻咽腔冷却は選択的に脳温を低下させ，早期に脳低温療法を施行することを目的に開発が進められている．

Ⅰ．虚血発生から神経細胞障害の始まりまで（図1）

脳への血流が絶たれると，秒単位で脳内酸素分圧が低下し[30)]，10～20秒でATPが半減する[15)]．ATPが減少することにより，神経細胞のATP依存性Kチャンネルが開きKイオンが細胞外へ放出され，神経細胞は過分極し脳波が停止する．ヒトでは意識消失に5～6秒[21)]，イヌでは脳波消失に約20秒を要する．

神経細胞のエネルギー消費の60％は脳波の産生に使用されているので，過分極はエネルギー消費を減少させるうえで好都合である．しかし，エネルギー供給が再開しなければ約2分でATPが枯渇し，膜電位を失う．脱分極によりグルタミン酸が放出され，神経細胞内にCaイオンが大量に流入する．正常状態では細胞内Caイオン濃度は細胞外の1/10,000以下にコントロールされてい

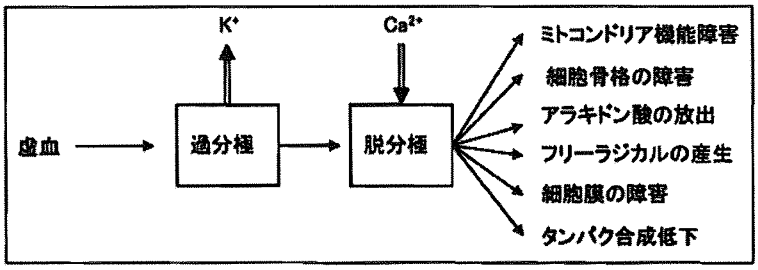

図1　虚血開始から脱分極まで
虚血発生後，数秒で脳内酸素分圧が低下し，嫌気性解糖が始まる．10～20秒で脳内ATP含量が半減する．Kイオンが放出され，神経細胞は過分極し，脳波が停止する．約2分でATPが枯渇し，神経細胞は脱分極する．Caイオンが流入し，さまざまな経路が活性化され，細胞は多臓器不全状態となる．

るが，脱分極により細胞内Caイオン濃度は約300倍上昇する29)．

大量に流入したCaイオンは細胞内の各種酵素を無秩序に活性化する．例えば，ホスホリパーゼの活性化はアラキドン酸を蓄積し23)，プロテアーゼの活性化は細胞骨格を障害する35)．また，Caイオンはミトコンドリア内に集積し，ミトコンドリア機能障害を引き起こす33)．脱分極で細胞内Caイオン濃度が上昇した後は，一つの経路を抑制しても治療効果を期待することはできない．細胞の多臓器不全状態である．

低体温療法は，特定の経路に対する治療法ではない．さまざまな経路を抑制する．現在わかっているだけでも以下の作用が報告されている29)．アポトーシスの抑制，興奮毒性の抑制，タンパク合成能の温存，浮腫の軽減，炎症の抑制，血管透過性の抑制，免疫応答の抑制，ミトコンドリア機能障害の抑制，フリーラジカル産生抑制などである．

このように，脳虚血後の神経細胞に対し脳低温療法は，包括的治療を提供している．

II．脳低温療法の臨床

動物実験では，脳低温療法は虚血性神経細胞障害に対し強い有効性を示しているが，ヒトで有効性が確認されているのは一部の疾患に限られている．現在までに臨床研究により解明されている事例を疾患別に示す．

1）心停止蘇生後

表1に示すように，心停止蘇生後患者（心原性）に対し2つの臨床研究（randomized controlled trial）が行われている．ヨーロッパで行われたHACA study1)と，オーストラリアのBernardら6)により行われた研究である．どちらの研究も患者の循環動態の回復確認後に比較的短時間（12～24時間）の全身冷却が施行され，大きな合併症を起こすことなく，6ヵ月後もしくは退院時の神経学的予後を有意に改善した．これらの結果から，心室細動による心停止蘇生後の成人患者に対し，32～34℃，12～24時間の脳低温療法を施行することが推奨されている．

表1　心停止蘇生後の神経学的予後に対する脳低温療法の臨床研究

著者	発表年	症例数	循環回復から冷却開始までの時間（分）	冷却法	目標温（℃）	冷却開始から目標温到達時間（分）	継続時間（時）	良好な神経学的回復を示す症例の割合		
								コントロール（%）	低体温（%）	統計
HACA study	2005	234	105	冷風	33±1	375	24	39	55	P=0.009
Bernard	2002	77	直後	アイスパック	33	120	12	26	49	P=0.046

表２　低酸素性虚血性脳症に対する脳低温療法の臨床研究

著　者	発表年	症例数	出生から冷却開始までの時間（分）	冷却法	目標温（℃）	冷却開始から目標温到達時間（分）	継続時間（時）	死亡or重度障害をきたす症例の割合		
								コントロール（%）	低体温（%）	統　計
Gluckman	2005	234	300	Cooling cap	直腸温 34-35	120	72	66	55	P=0.1
Shankaran	2005	239	300	Water blanket	食道音 33.5	90	72	62	44	P=0.01

現在，より早期に脳低温療法を導入することを目的とした治療法や，器具の開発が行われている．心拍再開直後の冷生理食塩水の急速静注[22]や，血管内冷却カテーテル[3, 11]はすでに臨床で使用が開始されている．咽頭冷却は，2009年度より臨床試験を開始予定である．今後，早期冷却デバイスや方法の評価が行われていくものと考えられる．

2）新生児

低酸素性虚血性脳症（hypoxic-ischemic encephalopathy）は，分娩時仮死が原因で発症する脳障害である．1,000例の満期出産に1例の割合で発生する[24]．表2に示すように，低酸素性虚血性脳症に対し2つの臨床研究が行われている．新生児は体重あたりの体表面積が広いため，保育器の加温機能を止め，cooling cap（8～12℃の冷水が循環するヘルメット型冷却装置）等を用いることで，比較的急速（90～120分）に目標温に到達している．どちらの研究も18～22ヵ月後の神経学的予後と死亡率は改善しており，有望な治療法として注目を集めている．

問題点は治療を開始するためのクライテリアの設定である．Gluckmanら[12]はApgarスコア，アシドーシス，神経学的所見に加え，脳波所見を指標に脳低温療法を施行している．一方Shankaranら[31]はApgarスコア，アシドーシス，神経学的所見を指標に脳低温療法を施行している．対象が新生児であるため，単一の指標ではなく複数の指標から総合的に判断する必要があり，経験が少ない施設では混乱する可能性がある．現在，より大規模な臨床研究[5]が進行中でありこの結果を待って，クライテリアの設定等コンセンサスが形成されていく必要がある[20, 29]．

3）頭部外傷

表3に示すように，頭部外傷に対しては多くの臨床研究[2, 8, 9, 25, 32]が行われている．しかし，研究により結果が大きく異なり，一定の見解が得られていない．

特に2001年に行われたCliftonら[9]の研究では，脳低温療法の有効性を見いだすことができなかった．この研究は症例数（392例）が多く，この結

表 3　頭部外傷に対する脳低温療法の臨床研究

著者	発表年	症例数	受傷から冷却開始までの時間（時）	冷却法	目標温（℃）	受傷or来院から目標温到達時間（時）	継続時間（時）	良好な神経学的回復を示す症例の割合		
								コントロール（%）	低体温（%）	統計
Clifton	1993	46		Water blanket	32-33	受傷から6	48	36	52	P=0.29
Marion	1997	82		Water blanket	32-33	受傷から10	24	38	73	P=0.04
Aibiki	2000	26	3-4	Surface cooling	32-33		72-96	36	80	P=0.04
Shiozaki	2001	91		Water blanket	34	来院から11.1	48	59	47	P=0.25
Clifton	2001	392	6	Surface cooling	33	受傷から8.4	48	43	43	P=0.79

果を覆すような大規模臨床研究は施行困難である．そのため，幾つかのメタアナリシスでは，「脳低温療法は頭部外傷後の神経学的予後を改善せず，肺炎を引き起こす危険性がある．臨床研究以外の目的で施行すべきでない」と結論づけている[4, 16)]．

一方，別の複数のメタアナリシスでは，臨床研究のサブグループ解析を行い，「脳低温療法は頭蓋内圧のコントロールには明らかに有効である．脳低温療法の経験豊富な施設で受傷後数時間以内に脳低温療法が開始され，48 時間以上継続されるならば，重症頭部外傷患者や頭蓋内圧亢進患者に対し有効性が期待できる」と結論づけている[7, 26, 28, 29)]．このように，頭部外傷に対する脳低温療法の有効性については，メタアナリシスにより微妙なスタンスの違いがある．

また 2008 年には，小児の頭部外傷に対する脳低温療法の臨床研究（症例数 225 例）が報告された[19)]．受傷 8 時間以内に 24 時間の脳低温療法（33 ℃）が施行されたが，脳低温療法群で神経学的予後が悪化する傾向が認められた．これらの報告より，少なくとも現状では，脳低温療法は頭部外傷患者の全例に行うべき治療法ではない．頭蓋内圧を指標に症例を選び施行すべきと考えられる．

4）脳梗塞

脳梗塞に対する脳低温療法の臨床研究（randomized controlled trial）は行われていない．動物実

表4　破裂性脳動脈瘤のクリッピング手術における脳低温療法の臨床研究

					良好な神経学的回復を示す症例の割合		
著　者	発表年	症例数	冷却法	目標温（℃）	コントロール（%）	低体温（%）	統　計
Todd	2005	1001	冷風	33	63	66	P=0.32

験では，再灌流を伴う脳梗塞モデルで脳低温療法の有効性が数多く報告されている．したがって，血栓溶解療法と組み合わせた治療法が今後検討される可能性はある．しかし現状では臨床データがなく，脳低温療法の脳梗塞に対する治療効果は不明である．

5）くも膜下出血

表4に示すように，2005年に破裂性脳動脈瘤のクリッピング手術中における脳低温療法の臨床研究が報告された7)．しかし有効性を見いだすことができず，術後感染症（血液培養陽性所見）は脳低温療法群で高頻度に認められた．クリッピング手術中の脳低温療法は，特に必要とされる症例（例えば，血流遮断時間が延長する可能性がある場合）に限って行われるべきと考えられる．

Ⅲ．脳冷却法

脳低温療法を行うための冷却法は，全身冷却法と選択的脳冷却法に大別できる（表5）．

1）全身冷却法

全身冷却法は，体表冷却法と血液冷却法に分けられる．

体表冷却法には送風ブランケット1)，冷却水ブランケット38)，アイスパック6)，冷却水が灌流するジェルパッド17)を用いる方法がある．送風ブランケット，冷却水ブランケット，アイスパックはランニングコストが安価で使用法が簡便であるが，目標温に達した後の温度のコントロール性が悪い．

ジェルパッドを用いる冷却法は，体温の低下が比較的早く，目標温に達した後の温度のコントロール性にも優れている18)．温度管理を行う医師，看護師の負担は大きく軽減される．ただしジェルパッド（消耗品）は高価でランニングコストはよくない．

血液冷却法には冷却した生理食塩液を輸注する方法22)と，血管内冷却カテーテルを用いて行う方法3, 31)がある．

4℃の生理食塩液の注入（最大2L）により体温は1.2℃低下し，輸液による肺うっ血や不整脈は発生しなかったと報告されている．方法が簡便なため，死亡率や神経学的予後に対する治療効果が認められれば急速に広まると思われる．

血管内冷却カテーテル3, 11)は最近商品化された冷却器具である．カテーテルは二重空を有し，血液に接している腔内に冷却液を灌流する構造になっている．カテーテルを大腿静脈から挿入し，下大静脈内で血液冷却を行う．血管内冷却カテー

表5　目標温（33 ～ 34℃）に到達するまでの時間と目標温に到達した後のコントロール性

	目標温に到達に要した時間 (33-34 °C)	目標温から0.2°C以上はずれた時間の割合(%) (文献18)
全身冷却法		
体表冷却法		
送風ブランケット	6 hours	74%
冷却水ブランケット	3.1 hours	51%
アイスパック	2 hours	
ジェルパッド	2.3 hours	44%
血管内冷却法		
血管内冷却カテーテル	1.3-3.5 hours	3%
選択的冷却法		
ヘルメット型冷却装置	1 - 3 hours	

テルを用いた方法では，体温の低下が早く，目標温に達した後の体温のコントロール性にも優れている18)．しかし，太いカテーテルを大腿静脈から挿入するため血腫や深部静脈血栓の発生が懸念され11)，安全性を含めた評価が必要である．

2）選択的脳冷却法

選択的脳冷却法には，ヘルメット型冷却装置と鼻咽腔冷却装置がある．

ヘルメット型冷却装置は頭部に装着し脳表を冷却する13)．海外では「Frigicap®」という商品名で市販されている．使用法は簡便であるが脳温の低下速度は緩やかである．また，皮質下の組織，特に虚血に脆弱な海馬や線条体の温度を脳表冷却でどこまで下げられるか，データがなく不明である．

鼻咽腔冷却は，鼻咽腔にカフを挿入し冷却液を灌流する方法である．図2に示すように，総頸動脈は鼻咽腔に接して上行していく．鼻咽腔を冷却すると，近接する総頸動脈が冷やされ，血行性に脳温を低下させることが可能である14)．この

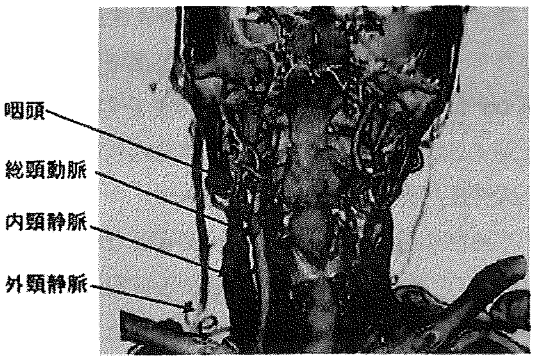

図2　頸部 3D-CT

総頸動脈は鼻腔，咽頭に接して走行している．一方，頸静脈は体表に接して走行している．鼻腔，咽頭を冷却すると頸動脈温が低下し，血行性に脳を冷却できる可能性がある．

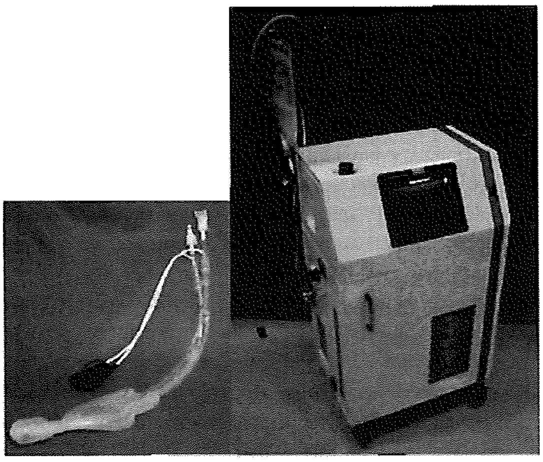

図 3　咽頭冷却カフと冷却水灌流装置
咽頭冷却カフは塩化ビニル製で圧力や温度センサーを備える．情報はリアルタイムに冷却水灌流装置で解析され，1 秒ごとに灌流圧や水温の制御が行われる．

方法は，脳を血行性に冷却するため，脳表だけでなく脳深部も同等に冷却することができる．また全身温に対する影響が小さいため，蘇生中から脳低温療法を開始できるメリットがある．動物実験では，蘇生開始と同時に鼻咽腔冷却を行うと，脳内グルタミン酸濃度の上昇が抑制され，わずか 20 分の冷却でも強い神経保護効果がある 36)．

現在，鼻咽腔冷却の開発は，スウェーデンのグループによる鼻腔冷却（両側鼻腔内にカフを挿入し冷却水を灌流）10) と，岡山大学と大研医器株式会社の共同開発による咽頭冷却（咽頭内にカフを挿入し冷却水を灌流）の研究が進められている．われわれのニホンザルを用いた研究では，蘇生時の脳温を 10 分で 2 ℃低下させることが可能であった．現在，厚生労働省の研究助成を得て，解剖体の 3D-CT 解析に基づいた咽頭冷却カフの開発や，安全機構を備えた冷却水灌流装置の開発を行っている（図 3）．2009 年度に蘇生時咽頭冷却の多施設臨床研究が予定されている．

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脳低温療法の現状と今後

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趣味：子供のラグビー観戦、釣り（全然釣れない）

はじめに

脳低温療法は、古くから行われてきた治療法である。以前は、体温を30℃以下に低下させていたため、合併症で死亡することが多く危険な治療法であった。1989年にBustoらが、軽度の脳低温療法でも強い神経保護効果があることを報告し1)、安全な脳低温療法の基礎が形成された。動物実験では、脳低温療法は虚血性神経細胞障害に対し強い有効性を示しているが、ヒトでも有効性が確認されているのは一部の疾患に限られている。現在までに臨床研究により解明されていることを疾患別にまとめた。

脳低温療法の現状

(1)心停止蘇生後

2002年、心停止蘇生後患者（心原性）に対する脳低温療法の臨床研究（randomized controlled trial）が報告された（Fig.1）。ヨーロッパのグループ（HACA study）2)は、心拍再開105分後より冷却を開始し、冷却開始6時間後に目標温（32～34℃）に達し24時間冷却を継続した。6ヵ月後の神経学的予後と死亡率で、有意な改善が脳低温療法群に認められた。オーストラリアのグループ3)は、心拍再開直後より冷却を開始し、冷却開始2時間後に目標温（33℃）に達し12時間冷却を継続した。退院時の神

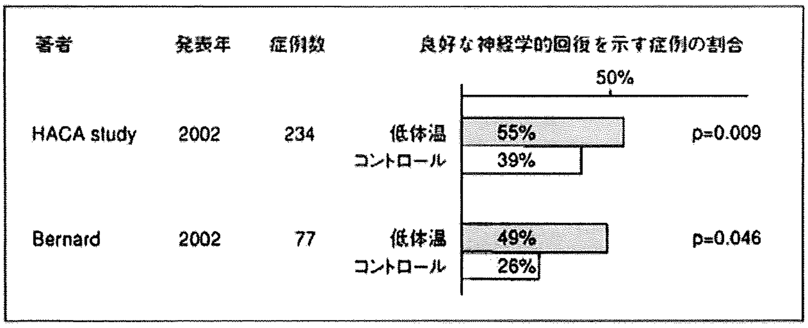

Fig.1. 心停止蘇生後の神経障害に対する脳低温療法の効果

経学的予後の比較で、有意な改善が脳低温療法群に認められた。このように、2つの臨床研究で有効性が認められたため、心室細動による心停止蘇生後の成人患者に32～34 ℃、12～24時間の脳低温療法を施行することが推奨されている。

(2)新生児の低酸素性虚血性脳症

低酸素性虚血性脳症(hypoxic-ischemic encephalopathy)は1,000例の満期出産に1例の割合で発生し、分娩時の仮死が主な原因である。近年、低酸素性虚血性脳症に対する脳低温療法の有効性が報告され注目を集めている。Gluckmanら4)は、生後6時間以内に冷却を開始し、2時間以内に目標温(34～35℃)に達し72時間冷却を継続した。Fig.2に示すように、18ヵ月後の神経学的予後と死亡率で脳低温療法群に改善傾向が認められた。Shankaranら5)は、生後6時間以内に冷却を開始し、90分以内に目標温(33.5℃)に達し72時間冷却を継続したところ、18～22ヵ月後の神経学的予後と死亡率で有意な改善を脳低温療法群に認めた。これらの結果より、脳低温療法は低酸素性虚血性脳症による死亡率を減少させ、生存者の神経学的障害を軽減させると認識されつつある。現在、大規模な臨床研究6)が進行中であり、それらの結果を待ってコンセンサスが形成されていくものと考えられる7,8)。

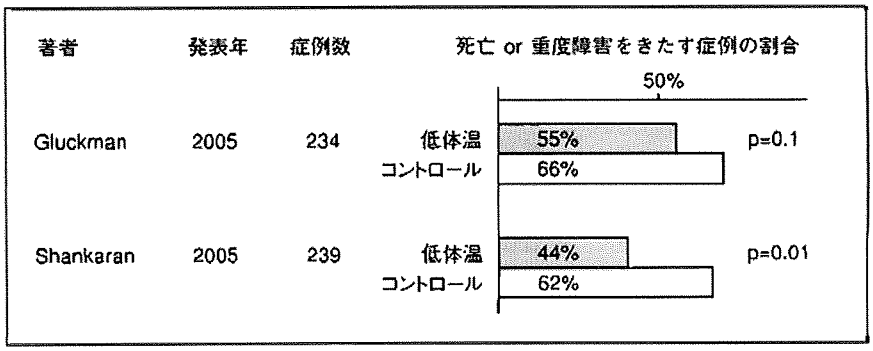

Fig.2. 新生児の低酸素性虚血性脳症に対する脳低温療法の効果

(3)頭部外傷

Fig.3に示すように、ヒトでは1993年にCliftonら9)が、脳低温療法で頭部外傷後の神経学的予後が改善傾向を示すことを報告した。その後、1997～2000年に*Marion*らやAibikiらの研究により、統計学的にも脳低温療法の有効性が示され、大規模な臨床研究が行われることとなった。しかし、2001年に行われたShiozakiら（症例数91例）やCliftonら（症例数392例）の大規模研究では全く有効性が示されなかった。メタアナリシスで臨床研究の横断的なサブグループ解析が行われ、「脳低温療法は頭蓋内圧のコントロールには有効である。脳低温療法の経験豊富な施設で受傷後数時間以内に脳低温療法が開始され、48時間以上継続されるならば、重症頭部外傷患者や頭蓋内圧亢進患者に対し、有効性が期待できる」と考察されている7,10～12)。少なくとも現状では、頭部外傷→直ちに脳低温療法とは言い難い。症例を選び、脳圧亢進患者の救命目的に施行するのが正しい選択だと思われる。

(4)脳梗塞

血栓溶解療法の有効性の検討に関心が集まり、脳低温療法はヒトでは全く検討されていない。そのため、重症脳梗塞患者の脳圧コントロール目的以外での脳低温療法の施行は勧められない13)。