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VALIDATION MEASUREMENTS AND COMPUTER SIMULATIONS OF THE NEWBORN'S BRAIN COOLING PROCESS

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Abstract: *The work presents the computational and experimental analysis of the neonate's brain cooling process. The brain cooling can be nowadays considered as a hypothermic therapy which allows to reduce significantly or even fully eliminate negative results of the hypoxic-ischaemic encephalopathy (HIE) which is still a relatively frequent problem encountered during childbirths (2 cases for every 1000 births).*

The fully 3-D real geometrical model of the newborn's body is built using Mimics software and the Design Modeler and utilizing available MRI and CT scans. The developed model is based on the Pennes bioheat equation which allows one to determine temperature field within all neonate's tissues. The blood perfusion rate, metabolic heat generation rate as well as arterial and venous blood temperature are all dependent on the tissue temperature. In order to determine proper values of the model parameters an attempt to experimental measurements and inverse analysis, based on the standard least-square method, is also carried out. Those measurements include experiments with the own thermal mannequin, specially designed stand to register the heat rate within a cooling cap and the thermographic camera. Obtained model parameters were also compared to the data obtained from neonatologists and medical literature.

To implement the whole model, the Ansys Fluent with its User Defined Function capability was used. Tuned model was then applied to simulate the neonates' brain cooling process with a good accuracy and to determine of the proper time of the therapy individual for a patient. Obtained results are also compared to real hypothermic therapy. In this way the new protocol of the therapy and particularly its rewarming phase can be established in the safe way.

1 INTRODUCTION

According to the data provided by the World Health Organization, perinatal hypoxemia is still a relatively frequent problem encountered during childbirths (2-4 cases for every 1000 births). The problem starts with improper blood circulation which causes insufficient transport of oxygen to the brain. At the same time insufficient cooling of the brain by blood causes increase of brain temperature. Question how serious are consequences of these dangerous conditions certainly depends first of all on how long neonate's brain was not sufficiently provided with the oxygen and how much its temperature raised. In many difficult situations, the hypoxic-ischaemic encephalopathy (HIE) can be developed. The selective brain cooling can be nowadays considered as a hypothermic therapy which allows significant reduction or even elimination of results of the hypoxic-ischaemic encephalopathy. It is, however, absolutely crucial that brain cooling of the neonate is initiated within 6 hours after delivery and that the body temperature of infants is kept in a consistent hypothermic range of 34oC to 35oC for at least 72 hours. At the same time, in order to mitigate the side effects of rapid change of tissue temperature during hypothermal therapy, deep body temperature should still be kept at a constant and secure level. This frequently requires thermal irradiating the rest of the body of the baby while its head should be cooled. Particularly important and difficult to maintain is the moment when the internal body thermoregulation centre is ready to intercept the control over the body temperature. An extensive review of those processes and relevant literature is offered by Łaszczyk and Nowak [1], [2].

Although this hypothermic therapy is already being applied for some years, it is still not quite clear how big should be a heat flux received by the cooling device from the newborn's head to maintain suitable temperature field inside the newborn's brain and throughout the entire body during the whole therapy period. Many doubts are also associated with a question what is the proper time of the hypothermic therapy. It should also be noticed that in case of cooling by use of the Cool Cap system, e.g. [3], the guidelines for rewarming phase are still not standardised and cooling parameters during this stage of treatment are set only manually. Therefore it is advisable to develop a reliable computational model of a typical newborn brain cooling process which after tuning could represent hypothermic therapy reasonably well and would offer possibilities of testing various therapeutic scenarios. It should be stressed that results of this kind of simulations could help, in a longer term, to identify the specific parameters to optimally tailor hypothermia therapy for individual newborns, and as a consequence - protect the life of neonates.

Heat transfer in the human brain and/or the whole human body has already been modelled and authors of these works used different levels of simplification in terms of geometry and in terms of mathematical description of the heat transfer processes. One of the first and the simplest model was proposed in 1998 by Nelson and Nunneley [4]. They treated head as a hemisphere with subsequent tissue layers (i.e. brain, skull and scalp). Then, geometric representations of the head in succeeding models evolved gradually tending to more realistic structures, e.g. [5]-[7]. In this context, a 3-D realistic anatomical voxel model of a neonate's head, proposed by Van Leeuwen et al. [8], and 3-D realistic model based on MR and CT scans, built by Łaszczyk and Nowak [1], [2], should be pointed out.

In terms of the mathematical description of heat transfer processes within the human tissue in the majority of works the entire neonate's body is divided into a number of segments like head, hand, foot, etc. and the Pennes bioheat equation [9] is adapted. It should, however, be stressed that the computational model of bioheat transfer processes proposed in [1] and [2] and used also in this work is essentially different from the models cited above. First of all, our

whole-body model applied herein is a full 3-D model (see Fig.1.), although, due to the symmetry, only the half of the neonate body is considered. From some cited works and particularly from Fiala [5], we borrowed only the idea of blood pool and the idea of geometrical segments [10] schematically shown in Fig.2. However, from the very beginning, we assume that those segments have really complex shapes and are smoothly connected to each other. As a consequence the temperature field within each segment is 3-D and heat is exchanged between neighbouring segments through their all interfaces.

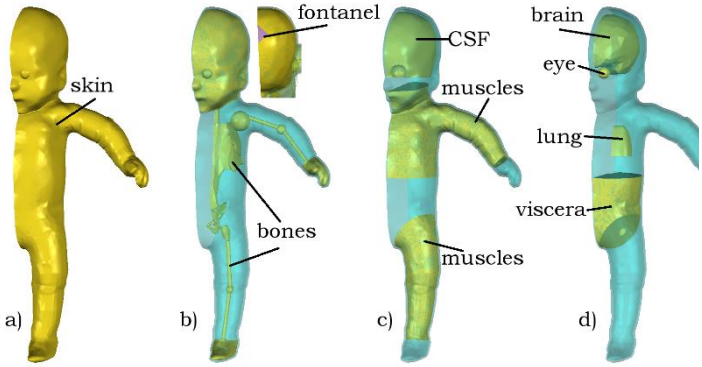

Figure 1: The 3D geometric model of the neonate's body.

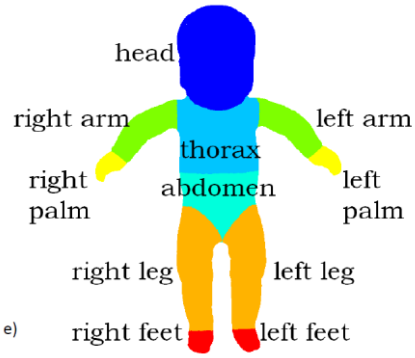

Figure 2 : Division of the body into sectors

In order to carry out computational solutions of the bioheat transfer in the newborn's body using above discussed model, the values of model parameters, i.e. blood perfusion rate, metabolic heat generation rate in particular tissues and an overall heat transfer coefficient on external skin need to be specified. Some of these parameters related to tissue properties have been subjects of the inverse analysis [1] and [2] while the overall heat transfer was measured using neonate thermal mannequin [11, 12, 13].

Equally important in this context are also boundary conditions, and particularly equation representing a heat transfer rate in the Cooling Cap. In this paper, the volume flow rate and temperatures of a cooling fluid flowing through a cooling cap are measured and recorded. This is the first attempt to monitor the time history of the heat flux rate transferred from the patient head to the cooling fluid during brain cooling process. This should help to understand the physics of the process better and fully control it.

2 BASIC MODEL EQUATIONS

The analysis of heat transfer processes during brain cooling should generally be carried out as a transient one, what eventually can lead to the steady-state. However, it should be noted that the heat capacity of the blood within one numerical cell is small comparing with the heat capacity of the tissue and as a consequence equations for arterial and vein blood temperature can be formulated as steady-state, but for the consecutive time steps.

As already mentioned, it is assumed that transient heat transfer in human tissues is governed by Pennes bioheat equation [5]:

$$\rho_t \, c_t \frac{\partial T_t}{\partial t} = \nabla \cdot \left(k_t \, \nabla^2 \, T_t \right) + \rho_b \, c_b \, \omega_t \, (T_{a,k} - T_t) + \zeta_t \, \dot{q}_{met,t} \tag{1}$$

where subscripts $()_t$, $()_b$ and $()_a$ refer to tissue, blood and artery, respectively. Symbol T stands for temperature (in K), k_t, in W/(mK), is a tissue thermal conductivity, ρ, kg/m^3, its

density while *c*, in J/(kgK) is a specific heat. Quantity $\dot{q}_{met,t}$, in W/m^3 represents a metabolism and is an amount of energy which is generated within a unit time and a unit volume of a tissue. Blood perfusion is marked by ω_t, in 1/s, time is depicted by *t*, in s, and ξ_t is a weighting factor varying between 0 and 1.

Obviously, for steady-state one can write:

$$0 = \nabla \cdot \left(k_t \nabla^2 T_t\right) + \rho_b c_b \omega_t (T_{a,k} - T_i) + \zeta_t \dot{q}_{met,t} \tag{2}$$

The blood perfusion rate and the metabolic heat rate are depended on the tissue temperature and they can be calculated in the following way:

$$\omega_t = \omega_{t,bas}\left(3^{(T_t - T_0)/10}\right) \tag{3}$$

$$\dot{q}_{met,t} = \dot{q}_{met,t,bas}\left(3^{(T_t - T_0)/10}\right) \tag{4}$$

where $\dot{q}_{met,t,bas}$, in W/m^3, $\omega_{t,bas}$, in 1/s, stand for the metabolic heat rate and the blood perfusion rate in the reference temperature T_0 equal to 310.15 K.

As already mentioned, the geometric model is divided into sectors: a head, a face, a neck, a shoulder, a forearm, a left palm, a leg, a left foot, a thorax and an abdomen. Each sector, identified by index $()_k$, has its own arterial blood temperature, $T_{a,k}$, (in K) vein blood temperature, $T_{v,k}$, (in K), and blood mass flow, $\dot{m}_k$, in kg/s. In the analysis it is assumed that mass flows of the artery and the vein bloods are equal. Each *k* sector is also divided into appropriate number of tissues, identified by index $()_j$, while index $()_i$ in the derived equations refers to a particular numerical cell.

Arterial temperature $T_{a,k}$ is calculated by the following relationship:

$$T_{a,k} = \frac{h_k \cdot T_{v,k} + \rho_b c_b T_p \sum_{j=1}^{J_k}\left[\omega_{j,k}\left(\sum_{i=1}^{N_{j,k}} V_{i,j,k}\right)\right]}{h_k + \rho_b c_b \sum_{j=1}^{J_k}\left[\omega_{j,k}\left(\sum_{i=1}^{N_{j,k}} V_{i,j,k}\right)\right]} \tag{12}$$

The heat transfer h_k accounts for the differences of the arterial and blood temperatures as dependent on the distance from the blood pool. Since the neonate's body which is generally small, comparing to an adult's body, it is assumed here that the value of h_k is generally small (almost equal to 0) for each segment.

It is assumed that the vein blood temperature $T_{v,i,j,k}$ leaving a given numerical cell *i* in tissue *j* in a segment *k* is equalled to the temperature of the considered numerical cell $T_{t,i,j,k}$. Additionally, the energy of the vein blood leaving the tissue *j* in a segment *k* is equalled to the total energy of the vein blood leaving all numerical cells in the tissue *j*, as well as that the heat capacity and density of blood is common for whole body, the temperature of the vein blood is expressed by:

$$T_{v,k} = \frac{\sum_{j=1}^{J_k} \omega_{j,k}\left[\sum_{i=1}^{N_{j,k}}\left(V_{i,j,k}\, T_{t,i,j,k}\right)\right]}{\sum_{j=1}^{J_k} \omega_{j,k}\left[\sum_{i=1}^{N_{j,k}} V_{i,j,k}\right]} \tag{13}$$

In the developed model it is assumed that the circulatory system contains the mixing spot called *the central blood pool* gathering the vein blood from all sectors and distributing the arterial blood to each sector. The temperature of the central blood pool, T_p, in K, is common for the whole body and is identified with the rectal temperature of the newborn.

In the central blood pool the blood from each segment is mixed. After some simple algebra manipulations [2] one can obtain the equation to determine blood pool temperature T_p which is an extension of result given by Fiala et. al., [5]:

$$T_p = \frac{\sum_{k=1}^{K}\left\{\frac{\dot{m}_k \cdot c_b{}^2 \rho_b \sum_{j=1}^{J_k} \omega_{j,k}\left[\sum_{i=1}^{N_{j,k}}\left(V_{i,j,k}\cdot T_{t,i,j,k}\right)\right]}{h_k + c_b \cdot \dot{m}_k}\right\}}{\sum_{k=1}^{K}\left\{\frac{\left(c_b \cdot \dot{m}_k\right)^2}{h_k + c_b \cdot \dot{m}_k}\right\}} \tag{14}$$

More details can be found in [1] and [2].

3 HYPOTHERMIC THERAPY AND MEASUREMENTS

As already mentioned, the hypothermic therapy should be initiated at most within 6 hours after delivery. Patient being prepared for the treatment is naked and he/she is losing heat to environment as it is visible in Fig.3. It can be expected that temperature at the abdomen/torso is typically quite even and approaches 34°C whilst at limbs values of temperatures is lower and equal to about 28°C. This fairly big temperature difference might be a surprise, but even for perfectly healthy neonate, temperature of his/her skin is not uniform. All protruding elements of the body like fingers at palm and foot, nose, shanks etc. are much colder than skin of remaining parts of the body. Temperature differences are absolutely noticeable and may even reach 3-4°C. This is confirmed by IR picture displayed in Fig.4.

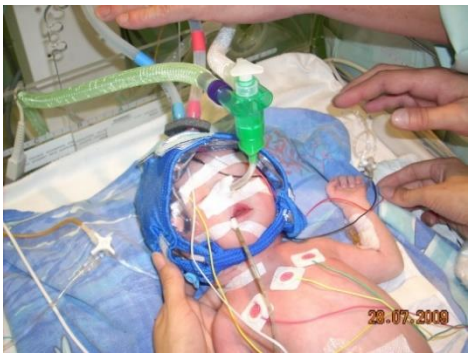

Figure 3: Patient with applied brain cooling therapy

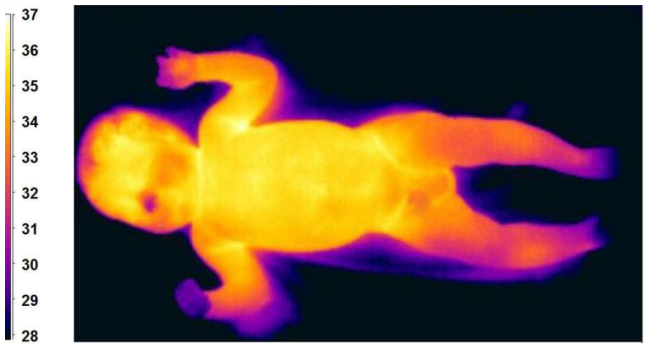

Figure 4: Temperature field of the baby's skin measured by thermographic camera

Then neonate's head is cooled using the cool cap supplied with cold water prepared by cooling centre as schematically shown in Fig.5. The rest of neonate's body is generally heated by heating mattress and being irradiated by radiant warmer (see Fig.6.). As a result temperature of the head decreases to about 28°C, whilst the temperature of the torso increases a little and

on the limbs rises even to about 37°C. It should be remembered that if the temperature on the skin surface of the head is such low, the temperature inside the neonate's brain is considerably higher but still at the required level. It is caused by the high thermal resistance of the bones, the high heat production of the brain and the current flow of the warm blood. This is confirmed by number of computer simulations, e.g. [2]. Exemplary results of this type of simulation are shown in Fig.7. a) and b) together with the temperature field of the central cross-section of the body in Fig.7. c).

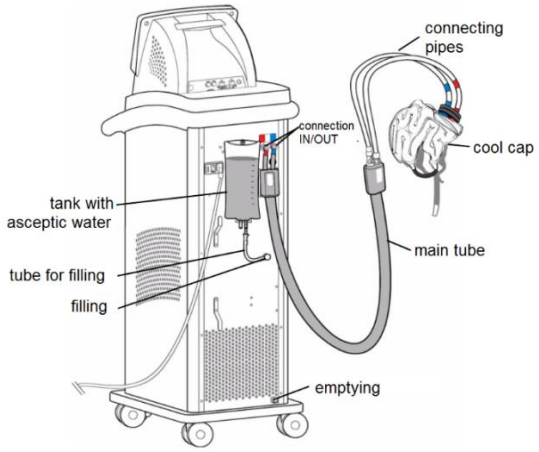

Figure 5: Accessories of Olympic Cool-Cap system [3].

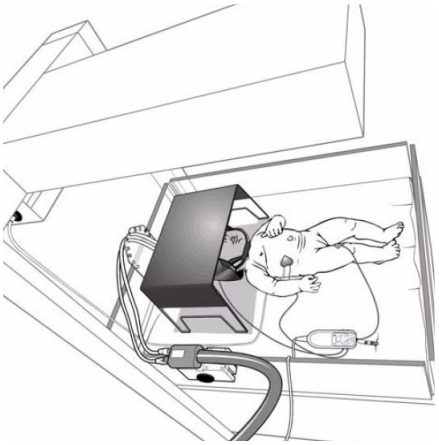

Figure 6: Thermal protection of the head.

The heat flux transferred from the brain to the cooling water flowing through the cooling cap is certainly not constant during therapy but depends on the water flow rate and its temperatures.

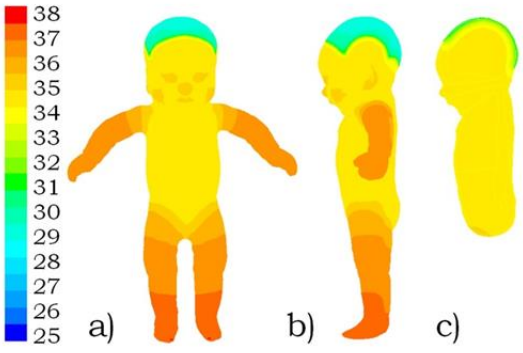

Figure 7: The temperature distribution (in °C) on the skin surface (a), at the left side (b) and on the central cross section (c) at the end of the cooling stage.

The Olympic Cool-Cap system originally controls only the average temperature of the cooling fluid and this is set by the neonatologist. Any other information about the performance of the system is not available. This is why special water flow meter equipped with temperature sensors has been designed and manufactured. This flow meter (shown in Fig.8.) is equipped with GSM system and allows one to monitor fluctuations of the heat flux in the brain cooling process even remotely using internet browser. However, data are secured by user account and password. In this way all computational analyses carried out during therapy can be made without any disturbance to the medical personnel.

Fig. 9. demonstrates how this special water flow meter equipped with the temperature sensors has been connected to one of IN/OUT ports of the cooling device. Hence, from the operation point of view, there are no differences for the nurses. There are no differences in the treatment process as well.

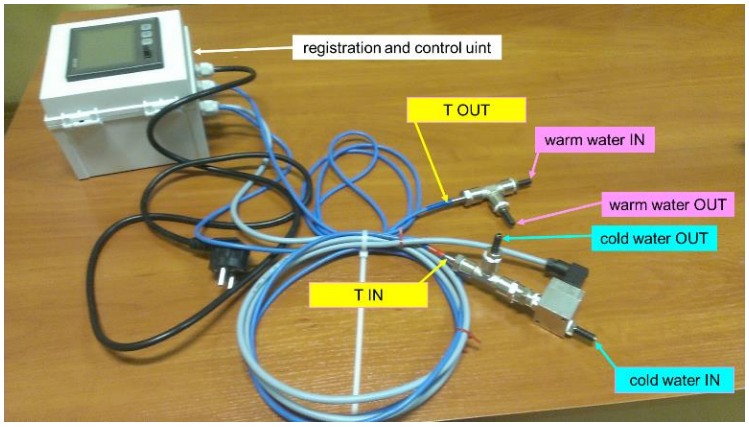

Figure 8: The water flow meter equipped with temperature sensors to monitor fluctuations of heat flux in the brain cooling process remotely

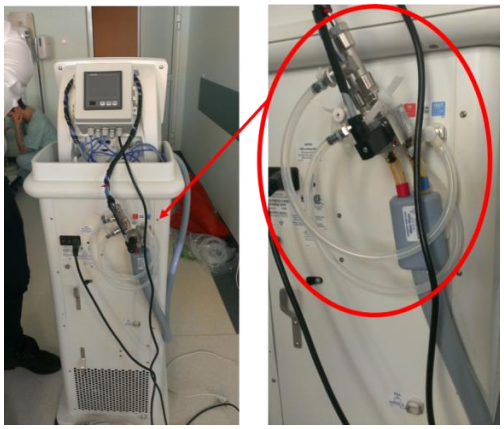

Figure 9: Cool Cap equipped with the water flow meter and temperature sensors

With the help of the water flow meter described in this paper, some measurements of the heat flux have been carried out and recorded remotely. They are discussed briefly in the next section.

Radiative component of heat transfer is determined utilizing apparent "radiative temperature" which was measured using so-called globe thermometer shown in Fig.10.

4 SELECTED RESULTS AND DISCUSSION

The water flow rate and temperatures of the cooling water have been measured in course of three hypothermic therapies, see Tab.1.

Figure 10: Globe thermometer measuring radiative temperature

ID	Date of birth	Actual mass in kg
D1	17.03.2017	2.79
D2	24.06.2017	2.90
D3	02.07.2017	2.14

Table 1: Basic data for considered three patients

The recorded history of variations of the cooling water temperatures in oC (red and dark blue curves), water flow rate in liters/min (green curve and scale on the right side) and heat rate in wats (light blue curve and scale on the left side) for patient N1 are presented in Fig.11. Simultaneously, variations of core temperature (light blue curve), the temperature of the skin over the abdomen (red curve) and temperature of the forehead (green curve), all in oC, have also been recorded and are shown in Fig.12. Curves in Fig.11. and 12 are plotted as one-hour means of measured values.

Fig.13 and 14 demonstrate analogous results for patient N2 while results for patient N3 are presented in Fig.15. and 16.

It should be noticed that core temperature is at the level of 34°C for all three patients, which was a desirable/expected temperature. The skin temperature is at the normal level, i.e. is around 36°C, again for all three patients. Some small disturbances can be observed for patient N3 between 15th and 25th hour of the therapy resulting in small overcooling of the lower part of the body. This was then compensated by radiant warmer.

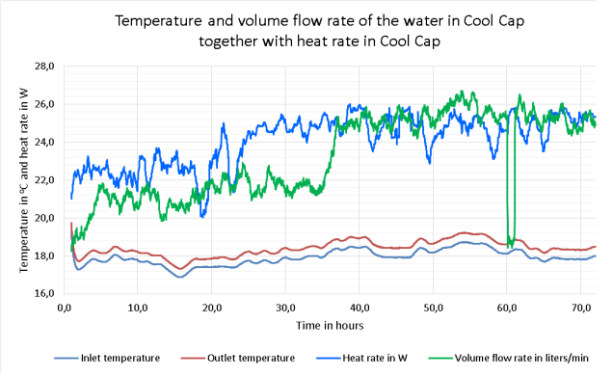

Figure 11: Measured temperatures and volume flow rate of the water in Cool Cap together with heat rate in Cool Cap – patient N1

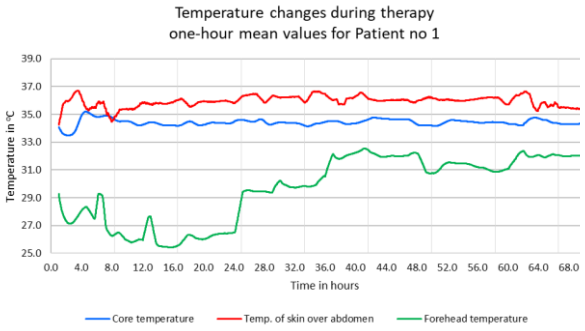

Figure 12: Variations of measured temperature during hypothermic therapy – patient N1

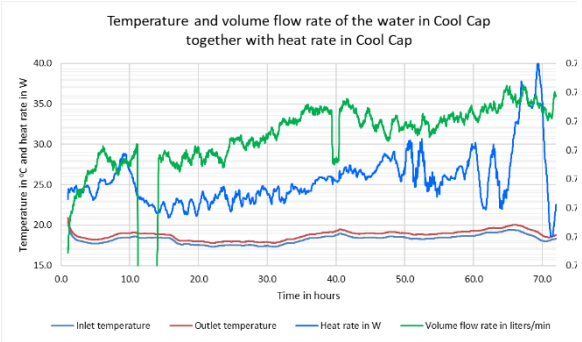

Figure 13: Measured temperatures and volume flow rate of the water in Cool Cap together with heat rate in Cool Cap – patient N2

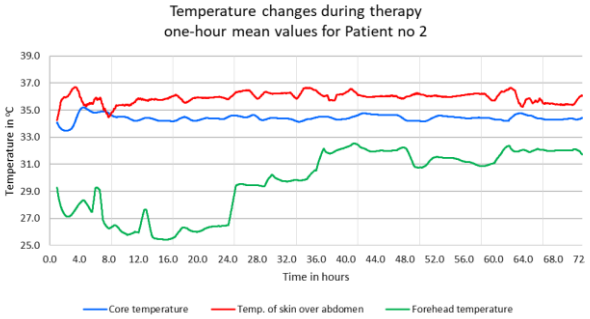

Figure 14: Variations of measured temperature during hypothermic therapy – patient N2

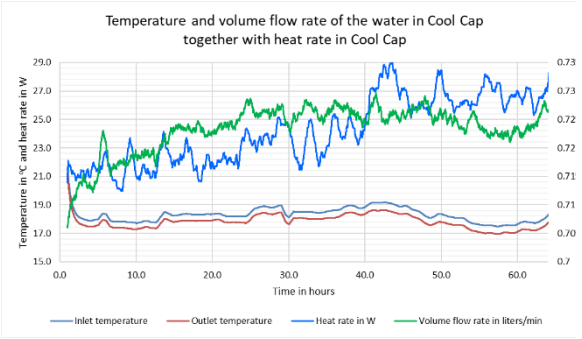

Figure 15: Measured temperatures and volume flow rate of the water in Cool Cap together with heat rate in Cool Cap – patient N3

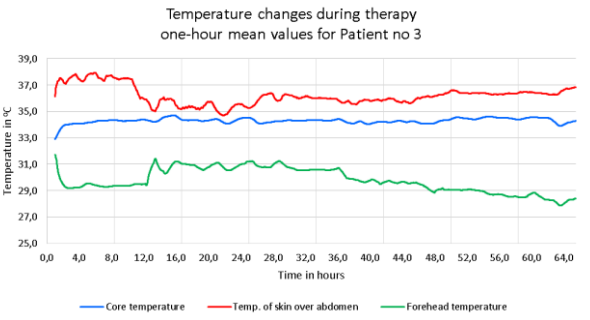

Figure 16: Variations of measured temperature during hypothermic therapy – patient N3

The temperature of the forehead for patients N1 and N2 are very similar while this temperature for patient N3 is essentially different. Reason for this different character of temperature variations is up to now not known, the more so heat rate for this patient is only slightly bigger than for patient N1 and visibly smaller than for patient N2. The one possible explanation can be associated with the clearly smaller weight of this patient, see Tab.1.

The rate of heat for all three patient is compared in Fig.17. It should be noticed that range of this quantity within the course of therapy is fairly similar for all three cases, at least between 10th and 45th hour of the therapy. Some more clear differences can be observed at the beginning of therapy. This is absolutely understandable since infants are transported to the hospital at different medical states. Much more difficult is to understand and explain those substantial fluctuations at the end of therapy. They will be analysed when more measurement data will be obtained.

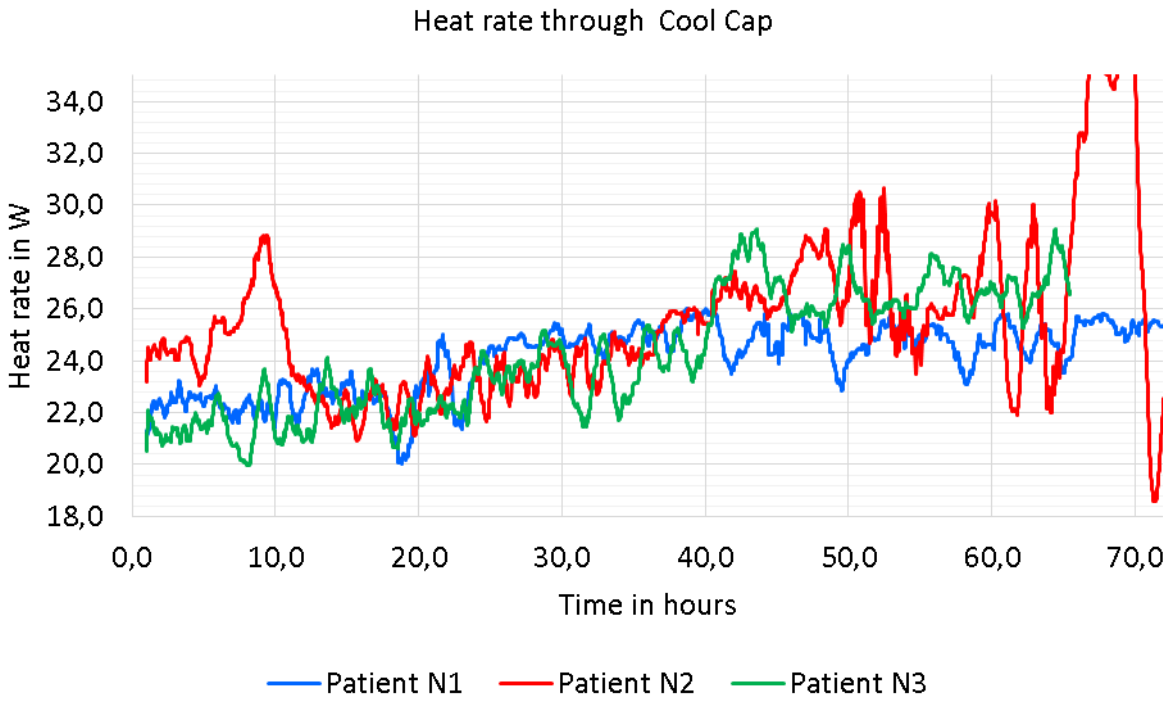

Figure 17: Comparison of the heat rate for all three patients

The measured values presented above are utilised to formulate convective boundary condition on the neonate's head. To make such boundary condition reliable many more experiments, as well as medical tests, are required.

8 CONCLUSIONS

The newborn's brain cooling can be considered nowadays as therapy to considerably reduce or even fully eliminate results of the hypoxic-ischaemic encephalopathy. The computer model of this therapy developed in the previous works cited in this paper requires reliable boundary

conditions. The most important boundary condition, i.e. the heat flux transported from a newborn's head to a cooling liquid was measured using specially designed measuring equipment. Identical measurements should certainly be repeated with subsequent patients and analysed from the statistical point of view.

No doubts, the therapy itself and its computational model still require a lot of medical trials due to some open questions such as the proper time of the cooling stage of the therapy, precise scenario of rewarming stage, the total time of rewarming, etc. Coupling developed a computational model with the series of experiments and processing results of measurements recorded during brain cooling treatment of real babies should allow verifying numerous research hypotheses related to that therapy. Such thorough examination of the newborn's brain cooling process and its analysis from different perspectives will allow deepening knowledge about hypothermic therapy.

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