

CLINICAL STUDY

Therapeutic hypothermia after out-of-hospital cardiac arrest with the target temperature 34–35 °C

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Abstract: *Background:* The objective of this study was to evaluate the impact of mild hypothermia (34–35 °C) on the final neurological outcome in patients after resuscitation from out-of-hospital cardiac arrest.

Methods: Forty three patients, admitted at University Hospital Brno after the out-of-hospital cardiac arrest, were included in the cohort study. The inclusion criteria were out-of-hospital cardiac arrest resulting from ventricular fibrillation or non-perfusing ventricular tachycardia as well as recovery of spontaneous circulation within 60 minutes after first symptoms. Blanketrol II (Cinninnatti Sub Zero, USA) water mattresses were used for cooling the patients. The temperature was maintained at 34–35 °C for 24 hours. Favorable neurological outcome was defined as a Pittsburgh cerebral-performance category 1 (good recovery) or 2 (moderate disability) on five-category scale.

Results: The required temperature was reached in all patients; the cooling rate was 0.8 ± 0.3 °C/hour. The time between the restoration of circulation and reaching the temperature of 35 °C was 119 ± 32 minutes. The time to induce the hypothermia (with the core body temperature below 35 °C) was 26 ± 2 hours. Good outcome at hospital discharge was achieved in 21 out of 43 (49 %) patients. Ten patients died in the hospital and two patients died after the discharge from the hospital, with the overall 6 months mortality being 28 %.

Conclusion: The study confirmed feasibility, safety and possible efficacy of the mild hypothermia (34–35 °C) in patients after the cardiac arrest. To evaluate whether the target temperature 34–35 °C is as beneficial as 32–34 °C; a randomised controlled trial design should be used (Tab. 4, Fig. 2, Ref. 17). Full Text (Free, PDF) www.bmj.sk.

Key words: cardiac arrest, ventricular fibrillation, therapeutic hypothermia.

The effectiveness of an induced hypothermia in patients resuscitated from cardiac arrest has been established and following recommendation has been made by the International Liaison Committee on Resuscitation: unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32–34 °C for 12 to 24 hours when the initial rhythm was ventricular fibrillation. Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest (1, 2, 3). The effectiveness of hypothermia is in its multifactor effect. A mild hypothermia improves and a mild hyperthermia aggravates the consequences of the ischemic neuronal impairment (4, 5). Hypothermia decreases metabolism and limits the release of excitatory amino acids, free radicals, and inhibits cytoskeleton axonal damage after the craniocerebral injury (6, 7, 8, 9). Having years of experience with applying the mild hypothermia (34–35 °C) on patients with the craniocerebral injuries, doctors decided to use it also on patients after the cardiac arrests (10). This milder

degree of hypothermia is more easily attainable, and also less undesirable side effects can be expected, especially concerning circulatory system. The objective of this study is to present the experience of University Hospital Brno in instituting therapeutic hypothermia and to find out the impact of the mild hypothermia 34–35 °C on the final neurological result of patients after the cardiac arrest.

Methods

After the Ethics Committee approval, patients admitted to the Department of Anaesthesiology, Resuscitation and Intensive Care, University Hospital Brno, in the years 2004–2006 were included in the cohort study. The admission criteria were out-of-hospital cardiac arrest resulting from ventricular fibrillation or nonperfusing ventricular tachycardia. The informed consent from the relatives or legal guardian of patients before recovery was waived by the Ethics Committee. If possible, the patients gave the informed consent after the discharge from the intensive care unit.

The inclusion criteria were following: cardiac arrest, age between 20–85 years, resuscitation initiation by an emergency physician within 15 minutes after the onset of the cardiac arrest, and recovery of spontaneous circulation within 60 minutes after first symptoms occurred. The study did not include patients with

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Tab. 1. Characteristic of patients.

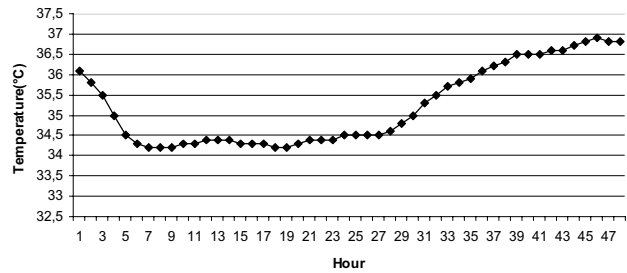
Number	43
Age – median (years)	67
– ranges	40 to 84
Female	7 (16 %)
Location of cardiac arrest	
– home	23 (53 %)
– public place	20 (47 %)
Basic life support provided by bystander	24 (56 %)
Total epinephrine dose (mg) (median)	3
– ranges	1 to 6
Interval between collapse and restoration of spontaneous circulation – min	
– median	20
– ranges	1 to 45

Tab. 2. Outcome after discharge according to the cerebral – performance category.

CPC 1	16
CPC 2	5
CPC 3	4
CPC 4	2

A cerebral performance category (CPC) of 1 indicates good cerebral performance. CPC 2 indicates moderate disability. CPC 3 indicates severe cerebral disability. CPC 4 indicates vegetative state.

circulatory arrest resulting from terminal disease, with the body core temperature on admission below 34 °C, with signs of coagulopathy and the patients manifesting the ingestion of medication affecting the central nervous system. Patients with continuous hypotension (mean arterial pressure less than 60mmHg for more than 30 minutes) after the restoration of circulation were also excluded. The patients were transported to this hospital by the emergency ambulances with physician who either continued in lay resuscitation, which had already started in the field, or who started an extended resuscitation after their arrival. In all cases, these measures included also orotracheal intubation and initiation of artificial lung ventilation. All patients were treated according to the exact procedures, which has been incorporated into standard procedures of the intensive care in this department. Sedation was introduced intravenously by administering intravenous midazolam (0.125 mg per kilogram of body weight per hour initially) and sufentanil (0.0005 mg per kilogram per hour initially), and the doses were adjusted as needed for 32 hours for the management of mechanical ventilation. Blanketrol II (Cincinnati Sub Zero, USA) water mattresses were used for cooling the patients, with one mattress under the body and the other on the top. The mattress temperature was set manually at 10 °C. The goal was to reach the body core temperature of 34–35 °C within three hours after restoration of circulation. After reaching the hypothermia, the temperature of the mattresses was set at 34 °C. Body core temperature was measured by a urinary catheter with a temperature sensor (Kendall). To prevent shivering, paralysis was induced by intravenous administration of pancu-

**Fig. 1. The mean bladder temperature curve.**

ronium (0.1 mg per kilogram) if needed. The temperature was maintained at 34–35 °C for 24 hours from the start of cooling, after which a controlled active re-warming started. The final neurological result of the treatment of the surviving patients was evaluated by an independent neurologist when the patients were ready for discharge. Favourable neurological outcome was defined as a Pittsburgh cerebral-performance category 1 (good recovery) or 2 (moderate disability) on five-category scale. The other categories were 3 (severe disability) and 4 (a vegetative state). Patients with a good recovery or moderate disability had sufficient cerebral function to live independently and work at least part-time. The 6 month overall mortality was evaluated, too. The values were expressed as the mean \pm standard deviation. The blood count and coagulation values were measured after admission to intensive care unit and then every twenty-four hour. The pneumonia was defined on the basis of clinical signs (fever, leukocytosis, purulent secretions, new infiltrates documented by chest radiography) and quantitative microbial cultures.

Results

Forty-three patients were eligible for the study over a period of 30 months. Demographical data of patients and further details are presented in the Table 1. The mean temperature of patients on admission to the emergency room was 36.1 ± 0.4 °C. The time interval between the restoration of circulation and the initiation of cooling was 95 ± 28 minutes. The required temperature in the range of 34–35 °C was reached in all patients; the rate of cooling was 0.8 ± 0.3 °C/hour. The time between the restoration of circulation and reaching the temperature 35 °C was 119 ± 32 minutes. The mean duration of the induced hypothermia (with the body core temperature below 35 °C) was 26 ± 2 hours. The time needed to reach normothermia was 373 ± 47 minutes (the mean bladder temperature curve is presented on the Figure 1). The average time to extubation was 78 hours and the patients were discharged from intensive care unit after 6 days. Good neurological outcome was achieved in 21 out of 43 (49 %) patients. Ten patients died in the hospital and two patients died after the release from the hospital, with the overall mortality 28 % (Tab. 3). Fifty eight percent required an infusion of epinephrine during the first 24 hours (the mean arterial pressure is described on the Figure 2). There were no clinically significant cardiac arrhyth-

Tab. 3. Neurologic outcome and mortality.

	No/total	No/(%)
Favorable neurologic outcome	21/43	(49 %)
Death	12/43	(28 %)
– in hospital	10	
– after discharge	2	

Tab. 4. Blood count and coagulation values.

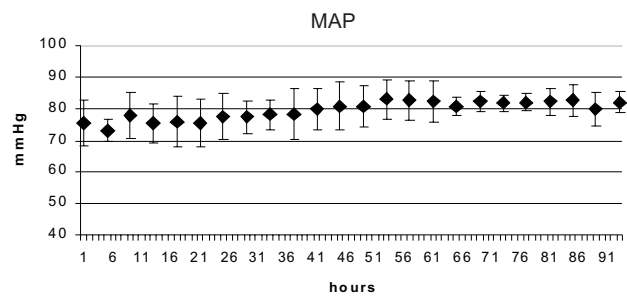
Hour	1	24	48
WBC ($10^9/L$)	7.6 ± 2.5	10.7 ± 4.1	10.8 ± 3.0
RBC ($10^9/L$)	4.3 ± 1.2	4.0 ± 0.8	4.0 ± 0.5
HB (g/L)	133 ± 18	125 ± 16	125 ± 18
HCT	0.38 ± 0.04	0.36 ± 0.03	0.36 ± 0.1
PLT ($10^9/L$)	191 ± 80	181 ± 70	196 ± 60
INR	1.28 ± 0.2	1.31 ± 0.3	1.23 ± 0.1
APTT	40.7 ± 8.2	43.2 ± 6.0	41.4 ± 6.0
FIB (g/L)	3.9 ± 0.4	3.0 ± 0.6	3.4 ± 0.5

WBC – white blood cells, RBC – red blood cells, HB – haemoglobin, HCT – haematocrit, PLT – platelet, INR – International Normalised Ratio, APTT – activated partial thromboplastin time

mias. The primary cause of death was considered as cardiac failure in 4 patients and the remaining deaths resulted from severe neurological injury. Complications occurred in 7 cases (16 %), where pneumonia was detected. Mucocutaneous haemorrhage occurred in one case; however, a probable cause may have been chronic thrombocytopenia. The cooling blankets did not cause skin damage. The blood count and coagulation values are summarized in the Table 4.

Discussion

Controlled hypothermia might be beneficial as a neuroprotective method against consequences of the ischemic insult in various groups of patients, mainly those after cardio-pulmonary resuscitation or cardiac arrest, in patients with craniocerebral injury, ischemic brain stroke, liver failure and in newborn babies with a brain hypoxia (11, 12, 13, 14, 15). There is certainly a number of factors that influence the final result of treatment in patients after cardiac arrest, beginning with the age and the underlying clinical condition. E.g. the average age of our patients was about 8 years higher than in studies by other European authors. The numbers of men and women, on the other hand, were very similar. Another important factor is the cause of the circulation arrest. The number of patient whom a bystander provided a basic life support (56 %) was slightly higher when compared to the European authors (48 %). It should be noted that an emergency ambulance with a physician is required by law to arrive at the place of the incident within fifteen minutes from the reporting. In the town of Brno, which is the main area of this hospital, the average arrival time is even shorter. In our patients, the average administered dose of epinephrin (3 mg) and the time before

**Fig. 2. The mean arterial pressure (MAP).**

the restoration of circulation (20 min) was almost the same as in the studies of the European authors (2).

A fundamental difference was in the procedure of application of an induced hypothermia. We used the technique of two cooling mattresses, which effectiveness had already been verified with another group of patients (10). The target temperature of body core of $34\text{--}35\text{ }^{\circ}\text{C}$ was attained in all cases in 119 minutes on average. There were no problems with the subsequent sustaining of this temperature for 24 hours. At present, we prefer inducing hypothermia also by intravenous infusion of iced solutions, as early introduction of hypothermia is of vital importance (16). For maintaining the required level of hypothermia we still use the method of cooling mattresses, as invasive techniques are, in our opinion, more suitable for the patients with longer-term decrease of the temperature. Regarding reheating, a slow active re-warming was selected with the average rate of $0.5\text{ }^{\circ}\text{C}$ per hour.

In clinical practice there are protocols using mainly a deeper hypothermia (around $32\text{ }^{\circ}\text{C}$). Mild hypothermia leads – through the sympathetic stimulation – to peripheral vasoconstriction, tachycardia and increased cardiac output. Moreover, the deeper stages of hypothermia can result in a progressive cardiovascular depression with subsequent hypoperfusion of tissues. A decrease of body temperature below $33\text{ }^{\circ}\text{C}$ causes the 1st degree atrio-ventricular block, and also an inversion of T-wave on the electrocardiogram. Several studies have confirmed a favorable effect of a milder hypothermia ($34\text{--}35\text{ }^{\circ}\text{C}$) on intracranial pressure, brain perfusion pressure and the final result of treatment of patients with severe head injuries, what was the reason why we wanted to verify its efficiency in the group of patients after a coronary arrest (10, 12, 17). Led by the above-mentioned considerations as well as by certain concerns about undesirable side effects of hypothermia on the circulatory system, we decided to use only a milder degree of hypothermia for a relatively long time period of 24 hours in this study. We also expected a lower risk of undesirable effects of hypothermia on coagulation system and a smaller risk of infection complications.

There are several limitations of this study. A cohort study certainly does not provide enough evidence for daily application of the mild hypothermia $34\text{--}35\text{ }^{\circ}\text{C}$ in all patients after cardiac arrest. It was not a randomised clinical study and it was not feasible to blind clinicians to the patients' treatment. The study was

done only in one hospital and the ages scale (47 years) is probably very large as well.

Therapeutic hypothermia with milder temperatures (34–35 °C) might also be beneficial for patients after out of hospital cardiac arrest. The percentage of patients with a good final neurological result of the treatment (49 %) was similar in our group of patients and the results of randomized studies of Australian and other European authors, where the numbers of patients with good final neurological result of treatment was 49 % and 55 %, when using induced hypothermia with the body core temperature between 32–34 °C (1, 2). In our group of patients, where mild hypothermia was used, mortality reached only 28 %, what is somewhat lower than in the above mentioned studies (51 % and 41 %). The study confirmed feasibility, safety and possible efficacy of the mild hypothermia 34–35 °C in patients after cardiac arrest. To evaluate whether the target temperature 34–35 °C is as beneficial as 32–34 °C, a randomised controlled trial design should be used.

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