

REVIEW / PRACA POGLĄDOWAJacek Szafranski¹, Małgorzata Szafranska², Marcin Gierach², Agnieszka Skowrońska², Władysław Sinkiewicz¹**THERAPEUTIC HYPOTHERMIA AFTER A CARDIAC ARREST
– BENEFITS, LIMITATIONS, CONTROVERSY****HIPOTERMIA TERAPEUTYCZNA PO NAGŁYM ZATRZYMANIU KRĄŻENIA
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Collegium Medicum in Bydgoszcz**S u m m a r y**

It is our intention to present in this work indications, contraindications and benefits regarding the application of therapeutic hypothermia in patients after cardiac arrest. Therapeutic hypothermia means lowering the internal temperature of the human body to 32-34 degree Celsius. It is a safe and efficient method increasing the patients' chances of survival and their neurological prognosis, especially if the

arrest was caused by cellular rhythm disorders. The efficiency of this treatment is confirmed by the American Heart Association and the European Resuscitation Board, which included it in the resuscitation guidelines for adults. We also describe the place of this treatment in valid resuscitation guidelines and pay attention to its mostly unknown potentialities and a few controversies.

S t r e s z c z e n i e

W pracy chcielibyśmy dokładnie przedstawić wskazania, przeciwwskazania oraz korzyści ze stosowania hipotermii terapeutycznej w leczeniu pacjentów po zatrzymaniu krążenia z przyczyn kardiologicznych.

Hipotermia terapeutyczna to obniżenie wewnętrznej temperatury ciała do 32-34 stopni Celcjusza. Jest to bezpieczna i efektywna metoda zwiększająca szansę na przeżycie oraz poprawiająca prognozy neurologiczne. Skuteczność tej metody jest potwierdzona przez Amerykań-

skie Towarzystwo Kardiologiczne oraz Europejską Komisję Resusytacyjną i została ona wprowadzona do wytycznych resusytacji dla dorosłych.

Przedstawiamy również miejsce hipotermii terapeutycznej w świetle aktualnych wytycznych dotyczących resusytacji, a także wskazujemy nowe, nieuwzględnione jeszcze potencjalne możliwości oraz liczne wątpliwości towarzyszące stosowaniu tej metody leczenia.

Key words: hypothermia, reanimation, sudden circulation arrest, therapeutic hypothermia**Słowa kluczowe:** hipotermia, reanimacja, nagłe zatrzymanie krążenia, hipotermia terapeutyczna**INTRODUCTION**

Therapeutic hypothermia used in patients after sudden circulation arrest is a safe and efficient method increasing the patients' chances of survival and their neurological prognosis, especially if the arrest was

caused by cellular rhythm disorders. The efficiency of this treatment is confirmed by the American Heart Association and the European Resuscitation Board, which included it in the resuscitation guidelines for

adults. However, it does not seem to be so certain in the case of patients in a state of pulseless electrical activity.

Hypothermia means decreasing the internal body temperature below 35 degree Celsius. Its theoretical basics were developed in the 1950s, when an Austrian anaesthesiologist of Czech descent published his book 'ABC of Resuscitation'. In the age of evidence-based medicine (EBM) we regard research of Australian scientists headed by Stephen A. Bernard, published in 2002 [1], and European ones headed by Michael Holzer [2] to be pioneers in that regard.

In the above research participated over 200 patients after sudden cardiac arrest (SCA) in the ventricular fibrillation or ventricular tachycardia mechanisms (VF/VT). Another inclusion criteria in the research was the hemodynamic stability of the patients after the successful reanimation in the condition of a coma (< 8 point on the Glasgow Coma Scale). Exclusion criteria were: presence of cardiogenic shock with the average blood pressure <60 mm Hg, hypoxemia, coma resulting from other causes than SCA, terminal disease, pregnancy or coagulopathy. The authors were the first to prove the decrease in mortality and adverse neurological changes in cardiac-arrest patients with VF or VT mechanisms treated by mild therapeutic hypothermia. On that basis this treatment became a standard procedure in treating SCA patients.

THERAPEUTIC HYPOTHERMIA APPLICATION PROTOCOL

Therapeutic hypothermia means lowering the internal temperature of the human body to 32-34 degree Celsius. It is composed of four stages: initial induction stage, sustaining stage, passive warming stage and normothermia stage.

The induction stage is cooling down the patient's body as soon as possible using various methods (table 1).

All the above methods are regarded as safe and efficient. However, invasive ones are quicker than the non-invasive ones. It is especially recommended and used widely in the pre-hospital care to inject NaCl solution cooled down to the temperature of 4 degree Celsius (0.9% NaCl solution, dosage 30 ml/kg mc [3]).

During the hypothermia sustaining stage the patient's body is maintained in the target temperature for 12 to 24 hours. During the passive warming stage the internal body temperature is slowly raised, not

quicker than 0.2 to 0.5 degree Celsius an hour. The last stage is to fight the fever, which can accompany this procedure and preventing the temperature from raising above 37 degree Celsius for the next 24 hours.

Table I. *Induction stage – methods*

Tabela I. *Etapy indukcji hipotermii – metody*

Hypothermia induction (indukcja hipotermii)	
Noninvasive methods (metody nieinwazyjne)	Invasive methods (metody inwazyjne)
Ice bags (worki z lodem)	Injecting cold fluids to peripheral or central veins (iniekcja zimnych płynów do obwodowego bądź centralnego układu żylnego)
Cooling blankets with cold water circulation (chłodzące okrycia z zimnym obiegiem wody)	Rinsing body cavities, bladder, anus Opłukiwanie jam ciała, pęcherza moczowego, odbytnicy
Cooling blankets with cold air circulation (chłodzące okrycia z zimnym obiegiem powietrza)	Extracorporeal circulation (krążenie pozustrojowe)

THERAPEUTIC HYPOTHERMIA SAFETY

Hypothermia complications in clinical research were relatively rare [4]. Those most often described in literature are: enlarged diuresis, vulnerability to infections (pneumonia, sepsis), dyselektrolitemia (hypomagnesemia, hypopotasemia), rhythm abnormalities (most often ventricular fibrillation with slow ventricular functionality, ventricular rhythm abnormalities), slow heart rate, muscle tremors, decreased heart projection (CO), clinically recognizable as lung edema, hypoglycaemia, thrombocytopenia, coagulation complications and disturbed medicine clearance. In Bernard's work the frequency of complications was not seriously greater in the group of patients treated with hypothermia than in the control group [1].

Moreover, it was observed during the research that in the group treated with hypothermia the end point (demise) occurred in 41% of patients, whereas in the group treated in the standard way it was 55% (p=0.02). Neurological complications in SCA patients with ventricular rhythm abnormalities were also more often in the control group (61% versus 45%, p=0.009) [2].

In another research it was noticed that patients undergoing the hypothermia had more chances of survival and less neurological complications, as well as spent less time in the intensive care unit – on the

average by 7 days – and did not require as much artificial ventilation [5].

Recently published research of German authors also confirmed the benefits of using therapeutic hypothermia on patients suffering from heart attack with ST–segment elevation. However, no increased mortality in the 30-day-period was observed, with statistically negligible tendency towards lesser long-term death rate during one-year period and noticeably improved neurological prognosis evaluated according to the Cerebral Performance Category (CPC) [6].

PLACE OF HYPOTHERMIA TREATMENT IN THE LIGHT OF CURRENT GUIDELINES

In the current European guidelines of 2010 therapeutic hypothermia is recommended as a routine procedure for all SCA patients, both in the case of ventricular heart rhythm abnormalities subject to defibrillation and in the pulseless electrical activity [7]. There is some difference between the guidelines of the European Resuscitation Board and those of the American Heart Association (AHA). In the latter, patients who in out-of-hospital conditions had cardiac arrest as a result of ventricular fibrillation or ventricular tachycardia should be treated with therapeutic hypothermia (recommended grade I, evidence level B). Patients with out-of-hospital SCA, with the pulseless electrical activity (PEA) or the asystole can be, according to the guidelines, treated with hypothermia to reduce neurological complications. However, in that case the recommended grade is much lower (IIb, evidence level B) [8]. The application of hypothermia for patients after the cardiac arrest in hospital has similarly low level of recommendations according to the AHA.

Published research evaluating the efficiency and safety of treating with hypothermia SCA patients with severe coronary syndromes confirms its benefits in preventing neurological complications and prognosis improvements [6, 9, 10, 11]. In Götberg's research patients with an acute STEMI eligible for primary PCI within 30 minutes their body temperatures were cooled to the target temperature of $<35^{\circ}\text{C}$ without allowing the induction of cooling to interfere with or prolong the door-to-balloon time for percutaneous coronary intervention (door-to-balloon time was 43 ± 7 minutes in the hypothermia group and 40 ± 6 minutes in the control group). Despite similar duration of ischemia, infarct size normalized to myocardium at risk was

reduced by 38% in the hypothermia group compared with the control group measured after 4 ± 2 days in a CMR examination. Similarly, there was a significant decrease in release of Troponin T in the hypothermia group (43 % reduction of peak Troponin T release) [12]. 2 patients had ventricular arrhythmia during the early post infarction period in the control group, whereas none in hypothermia group. No heart failure was seen in the hypothermia group and 3 patients in the normothermia group had clinical signs of heart failure.

Some investigators suggest that these outcomes appear to cardioprotection and prevention of reperfusion injury. If these results are confirmed in larger trials cooling in STEMI patients will be the first widely accepted form of successful controlled reperfusion preventing reperfusion injury except for hypothermia following cardiac arrest [13, 14].

The latest guidelines of the AHA dedicated to the pre-hospital procedures in case of Adult Advanced Cardiovascular Life Support recommend that patients after cardiac arrest and successful reanimation are directed to reference centres. Such hospitals should ensure constant care in the intensive care units, including round-the-clock neurological control. They should also be prepared to administer invasive reperfusion treatments and therapeutic hypothermia [15].

CONTROVERSIES

In spite of many proofs of mild therapeutic hypothermia benefits and its safety, there are still important unresolved issues of how to apply it. A typical example is the presence of ventricular rhythm abnormalities. It is known that ischemia, reperfusion, and decreasing internal body temperature contribute to ventricular rhythm abnormalities. Also, hypothermia prolongs the QT corrected interval value or, as mentioned, causes or intensifies bradyrhythmia. During hypothermia the progression of conduction abnormalities may also occur. It is important, because basic medications in prevention and treatment of ventricular heart rhythm abnormalities, such as beta blockers, also slow down heart rate. Amiodaron, often used in rhythm abnormalities, also prolongs the QT interval value. During the animal research the efficiency of this medicine in hypothermia was not confirmed [16, 17].

Similarly to hypothermia, beta blockers and the intravenous application of magnesium used in treating ventricular heart rhythm abnormalities in the long QT interval cause and intensify both bradyrhythmia and conduction disorders. Values of the QT corrected interval are in direct proportion to the degree of decreased body temperature [18], so in the case of ventricular rhythm abnormalities secondary to the prolonged QT interval, it is proposed to warm up the patient's body 1 degree Celsius more and inject her with magnesium solution [18]. However, there are no uniform procedure guidelines based on scientific evidence how to monitor and treat ventricular disorders during the application of therapeutic hypothermia.

Another difficult problem is defibrillation and medicine action in hypothermia patients. No clinical research has been so far made on people to prove their efficiency. Experiments on animals gave conflicted results, necessitating further research [19, 20].

Hypothermia changes the metabolism of the whole organism, including the clearance of many medications, e.g. clopidogrel. In the unique research made so far, patients who received saturating dosage of clopidogrel (300 do 600 mg) after sudden cardiac arrest secondary to the severe coronary syndrome (also treated with therapeutic hypothermia), did not undergo essential platelet function arrest (defined as platelet reactivity index <0.5) during the first 24 hours. On the third day, platelet function arrest was achieved in 1/3 of the patients [21]. Likewise, the safety of using double antiplatelet treatment has to be verified through big clinical research, as hypothermia increases the risk of bleeding, especially in the case of thrombocytopenia [2].

In the light of recently published results of a large French SCA patient registry, in the pulseless electric activity or asystole mechanisms, the application of therapeutic hypothermia became debatable. The research included 1145 cases of successful out-of-hospital reanimation. The percentage of SCA in ventricular rhythm abnormalities was 62%, of which 65% of patients were treated with mild therapeutic hypothermia. The research confirmed earlier reports of the beneficial influence of hypothermia on mortality and neurological complications after SCA. However, in the group of SCA patients in the PEA and asystole mechanisms no improvement was observed; on the contrary, the results seemed actually worse [22].

REVIEW

Summing up, the application of therapeutic hypothermia in patients after sudden cardiac arrest in the VF/VT mechanisms is recommended in the light of the guidelines of the European Resuscitation Board and those of the American Heart Association. Unequivocal benefits of that treatment were proved. It is expected that further randomized, many-unit clinical research will be performed to evaluate its safety and efficiency in SCA patients in the OZW mechanism.

Unfortunately, in Poland therapeutic hypothermia is still largely unknown, not only because it is quite expensive and difficult to perform, but also because the knowledge of this procedure, its potentialities, indications and benefits among doctors is insufficient.

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