



THERAPEUTIC HYPOTHERMIA AS TARGETED TEMPERATURE MANAGEMENT IN THE TREATMENT OF PATIENTS AFTER SUDDEN CARDIAC ARREST (SCA) – A NARRATIVE REVIEW

HIPOTERMIA TERAPEUTYCZNA JAKO OZIĘBIENIE I UTRZYMANIE DOCELOWEJ TEMPERATURY CIAŁA W LECZENIU PACJENTÓW PO NAGŁYM ZATRZYMANIU KRAŻENIA (NZK) – PRZEGLĄD NARRACYJNY

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ABSTRACT

Therapeutic hypothermia is one of the few interventions that improve survival after sudden cardiac arrest (SCA) with good neurological outcome. Nowadays, mild therapeutic hypothermia (MTH) is a well-documented method in emergency medicine.

Current guidelines for cardiopulmonary resuscitation recommend this method in patients after the return of spontaneous circulation. Low temperature causes some adaptive responses, e.g. a protective effect in the central nervous system (CNS) and improved neurological status. As a therapeutic method, it is usually applied in the form of mild therapeutic hypothermia (MTH), currently referred to as targeted temperature management (TTM, 32–36°C). The aim of the present narrative review was to present the current data and trends regarding the use of TTM in Poland compared to other selected countries. The literature analysis has revealed a relatively positive trend in terms of the method popularity and implementation. However, recent reports clearly demonstrate that it is applied highly too cautiously and insufficiently in Poland compared to other European countries. This is of particular concern as the instances where hypothermia has been used in therapy show that it is truly effective in patients after SCA.

KEYWORDS: mild therapeutic hypothermia, sudden cardiac arrest, emergency interventions.

STRESZCZENIE

Hipotermia terapeutyczna jest jedną z niewielu metod poprawiających szanse przeżycia po nagłym zatrzymaniu krążenia (NZK) z dobrym statusem neurologicznym. Obecne wytyczne resuscytacji krążeniowo-oddechowej rekomendują tę metodę u pacjentów, u których przywrócono spontaniczne krążenie krwi. Niska temperatura wywołuje wiele adaptacyjnych odpowiedzi organizmu, m.in. chroni ośrodkowy układ nerwowy (OUN), zmniejszając tym samym ryzyko dysfunkcji o charakterze neurologicznym. Jako metodę terapeutyczną najczęściej postrzega się łagodną hipotermię terapeutyczną (MTH), która według obecnej nomenklatury jest oziębieniem i utrzymaniem docelowej temperatury ciała (TTM, 32–36°C). Celem pracy było przedstawienie aktualnych danych i występujących trendów, dotyczących stosowania TTM w Polsce na tle innych krajów. Analizy bibliograficzne wskazują na relatywnie pozytywny trend popularności i stosowania metody hipotermii terapeutycznej. Jednak ostatnie lata wyraźnie pokazują, że jest ona stosowana bardzo ostrożnie i niedostatecznie często. Polska wypada błędnie na tle krajów europejskich. Ponadto przypadki zastosowania hipotermii w terapii wskazują efektywność u pacjentów po NZK w praktyce klinicznej.

SŁOWA KLUCZOWE: łagodna hipotermia terapeutyczna, nagłe zatrzymanie krążenia, interwencje ratunkowe.

Introduction

Historically, using hypothermia as a potential method of preventing and/or reducing secondary damage resulting from sudden cardiac arrest (SCA) first occurred as early as the 1940s [1, 2]. Approximately ten years later, a possibility for clinical use of the therapy was suggest-

ed [3]. At that time, an exceptional study was conducted that included 19 patients resuscitated after perioperative cardiac arrest. Each patient's thorax was opened, and the asystole or fibrillation of the heart was noted. The patients were cooled using blankets containing a circulating coolant. Their body temperature was

maintained at 31–32°C. When there was no improvement, they were gradually withdrawn from hypothermia. Among the cooled survivors, the duration of hypothermia ranged from 34 to 84 hours, while in the non-survivors, it ranged from 3 hours to 8 days. Seven patients did not receive hypothermia, and only one of them survived. Six out of 12 cooled patients survived, suggesting an improvement in the survival rate from 14% to 50% [3]. However, additional studies with more patients were about to occur.

Since 1960, researchers have implemented the method in clinical practice with indications of positive effects of the cooling of the body [4, 5]. In 2012, in Poland, they created the Polish Registry of Hypothermia. However, Polish experience of using hypothermia is still limited.

In this narrative review, we would like to present the impact of therapeutic hypothermia on the human body, the benefits of implementing targeted temperature management (TTM) and to show the adaptation of this method in Poland.

Evidence-based selected physiological effects and benefits of therapeutic hypothermia

Low temperature causes several adaptive reactions in humans, beginning when the body's internal temperature is lower than 36.5°C. The adaptive responses may be classified as behavioural or vegetative. The duration of exposure and the intensity of lower temperature affects the body, as well as nervous and humoral responses to stress, whereas changes in the rate of depletion of energy reserves cause organic and metabolic reactions [6–8].

Fortunately, the human organism is evolutionarily equipped with a very efficient mechanism of normothermia. Hypothalamic thermoregulation areas, that is, preoptic-anterior hypothalamus (PAH) and dorsomedial hypothalamus (DMH) [9, 10], control both the production (in metabolic processes) and dissipation of heat. An essential task is the thermal balance of central internal organs – *core*. The remaining peripheral parts of the body – *shell* – change the temperature in various oscillations and act as a buffer for giving off or accumulating heat. This happens via thermoregulatory arterio-venous anastomoses [11]. The metabolic activity of muscles also plays a significant role, resulting in 50–100% of heat production, in improving thermal balance [12].

It has been shown in preclinical studies that hypothermia influences trophic factors in the central nervous system (CNS), such as brain-derived neurotrophic factor (BDNF) [13] and vascular endothelial growth factor (VEGF), resulting in intensified angiogenesis [14]. In addition, a decrease in glutamate-induced excitotox-

icity has been observed [15]. These data suggest that hypothermia acts anti-apoptotically on neural cells, as confirmed the *in vitro* studies by Yang et al. [16] and Khar et al. [17].

Inhibition of pro-apoptotic signalling pathways via activation of tumour necrosis factor (TNF- α) and caspase (CASPs) was observed [18]. Moreover, some data suggest that hypothermia can modulate mitogen-activated protein kinases (MAPKs) and suppress protein 53 (p53), calpains, cathepsins, granzymes and apoptosis-inducing factor (AIF) concentrations [18–21]. A simultaneous elevation of the anti-apoptotic factors C-epsilon protein kinase (PKC ϵ), serine-threonine kinase and Bcl-2 was observed [18, 21]. Moreover, hypothermia had a normalizing effect on metabolic aberrations accompanying SCA, such as decreased lactate concentration, reduced intensity of cellular acidosis and improved carbohydrate metabolism in CNS while maintaining the proper level of glucose. In addition, it has been shown to reduce endothelial dysfunction and stabilize the blood-brain barrier function, thus preventing ischemic damage [22, 23]. On the other hand, excessive cooling of the body may cause complications. It should be emphasized that severe hypothermia may cause choreoathetosis [24] and disorders of lipid [25] and carbohydrate metabolism [26]. Knocker [27] observed that these alterations led to increased infiltration of internal organs with lipids, which can result in death.

Targeted temperature management with therapeutic hypothermia

Until recently, therapeutic hypothermia was understood as mild hypothermia, where body temperature ranged from 32 to 35°C. Some current literature suggests that the optimal temperature is 32 to 34°C [28, 29]. However, these observations focused only on visible neuroprotective actions. Generally, mild therapeutic hypothermia (MTH) was considered beneficial based on meta-analyses from randomised controlled trials comparing therapeutic hypothermia to no cooling [30]. MTH was the only treatment confirmed to improve the effectiveness of SCA patient therapy [31]. The European Society of Cardiology and European and Poland Resuscitation Councils recommended this procedure for SCA patients [32, 33]. As shown, they should start it as soon as possible after SCA. Currently, some specialists have noted that fast implementation of MTH results in better CNS condition (fewer lesions) [34]. Unfortunately, the target cooling temperature remains unknown. Lopez-de-Sa et al. [35] compared two groups of patients treated with hypothermia (to 32°C or 34°C) and concluded that a higher neurological improvement occurred with 32°C hypothermia. Alternatively, Nielsen et al. [36] showed

no difference in the improvement of neurological status in patients from a group cooled to 33°C compared to a group cooled to 36°C. According to the results of a study by Heaton from the Hypothermia After Cardiac Arrest Study Group (HACA), in the patients who have been restored after an SCA incident due to ventricular fibrillation, systemic cooling to 32°C and 34°C for 24 hours increased the chance of positive neurological examination results compared to the normothermic procedure [37]. Bernard et al. [38] achieved results similar to those described in the present study. However, there are reports that have shown a lack of improvement in the neurological status of patients. In the study by Clifton et al. [39], no beneficial effect of therapeutic hypothermia in patients after traumatic brain injury (acute) was noted. It is possible that different pathogenesis of CNS damage occurred in this group. Potentially, if the cooling of a patient's body had been initiated too late, it could have remained ineffective. It should be noted that differences in the intensity of cooling may also confound the results. The results of an observational study by Nurnberger et al. [34] showed that rapid MTH in patients after SCA improved the chances of survival. Similarly, such observations are confirmed by, e.g. Wolff et al. [40] and Mooney et al. [41].

More recent data from a meta-analysis by Kalra et al. [42] do not demonstrate any alterations in all-cause mortality rates in the hypothermia versus normothermia comparison. The researchers have not found any difference in the rates of favourable neurologic outcomes. Nowadays, similar opinions and multiple studies result in the implementation of newer guidelines and recommendations. Hence, the American Heart Association guidelines now suggest TTM should be used after strictly outlining a therapeutic hypothermia strategy [43].

Phases of TTM with therapeutic hypothermia

The use of therapeutic hypothermia comprises three phases, that is, induction, maintenance and heating [7, 33]. Induction (cooling) should start as soon as possible after the return of hemodynamic functions. It should aim for the fastest possible target temperature [33]. The maintenance of the target temperature is also a very critical phase, where brain temperature is correlated with the temperature of the urinary bladder [44]. It should always be kept in mind that excessive cooling increases the risk of arrhythmia, coagulopathy and infections [45].

Body cooling techniques

The most common techniques used are non-invasive (surface) and invasive cooling. Surface techniques are

widely available, relatively inexpensive, and their use is not dependent on hospital conditions. These include ice bags, cooling or air blankets, frozen compresses and cooling helmets (air or cold water) [46]. It is not surprising that the disadvantages of these techniques include the duration of time to achieve a certain temperature. Using non-invasive cooling systems based on IT technologies is preferable, including electronic control, such as Banketrol III, Cincinnati Sub-Zero, CritiCool, Medical ThermoRegulation Expertise, Arctic Sun and Bard [47]. Invasive body cooling techniques may be classified as experimental, commonly used and historical ones. Obviously, the commonly used and experimental techniques are currently employed in medical science.

The invasive techniques allow for a rapid reduction of body temperature but can only be used in Intensive Care Units (ICUs). These include intravenous administration of cold fluids (solutions), body cavity rinsing, urinary bladder and rectum rinsing, extracorporeal circulation, cold infusions into the carotid artery, perfusion from the carotid artery with extracorporeal blood-cooling and peritoneal rinsing [46].

At present, the most widely used invasive technique is intravenous administration (peripheral or central veins) of cold 0.9% NaCl, Ringer's or Hartmann's solutions (4°C).

An extremely interesting solution is the use of extracorporeal membrane oxygenation (ECMO), which enables quick reduction of heat, down to 6°C per one hour.

This technique is currently the most efficient in lowering body temperature; however, technical and logistic limitations decrease its applicability to selected ICUs [4]. Recently, Alves and Mady [48] have analyzed the techniques of body cooling presented. Interestingly, combinations of invasive and non-invasive techniques turned out to be the most effective.

TTM with therapeutic hypothermia in Poland and other European countries

An analysis of the use of TTM in Polish ICUs from 2005 showed that only 7.6% of units used the therapeutic procedure in patients after SCA [49]. Interestingly, in 2010 the usage increased to 21% of ICUs in Poland, declaring the use of this method [50]. In comparison, TTM with hypothermia was used in 41% of ICUs in the Czech Republic [51], and in Finland, hypothermia was used in the treatment of 61% of patients after SCA in 2006 [52]. The widest application was observed in the United Kingdom (UK), where as many as 85.6% of ICUs used TTM after SCA cases, as reported by Binks and Nolan [53].

Recently, Kołtowski et al. [54] have shown that therapeutic hypothermia is not a common procedure in Poland. Regardless of the passage of time, the method

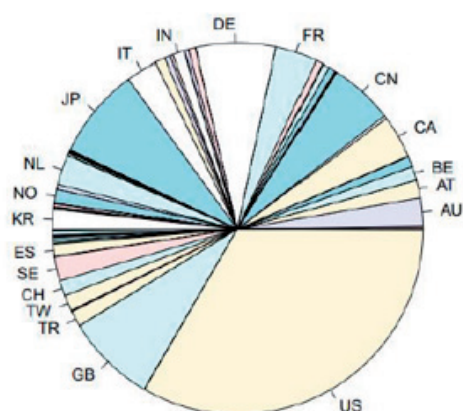
application oscillated around 30% ICUs. The factors that contribute to this condition mainly include poor knowledge and lack of experience.

It should be mentioned that TTM is a term most commonly understood as maintenance of the body's core temperature between 32°C and 36°C, and therefore, it covers a wider range than mild therapeutic hypothermia (MTH). While the clinical outcome of MTH has been proved in several studies, the impact of maintaining patient temperatures as TTM remains less clear.

Gradual spread (however discontinued and insufficient) of the therapeutic hypothermia method over the last years has also been confirmed by the trend analysis using MEDLINE tools (PubMed) (**Figure 1**). In fact, Poland was classified under the chart's sensitivity, which is a disturbing observation nowadays. The Polish Register of Therapeutic Hypothermia was already established on July 25, 2012. It is an institution that collects results and evidence-based data related to MTH. It seems that the insufficient use of MTH is evidenced by the lack of scientific publications showing the scope of application of this method in Polish ICUs. It is also revealed by the fact that MTH treatment is still described as an "innovative method", whereas over the years, this method should have become standard—not innovative—in post-resuscitative medicine.

dia). After taking the history, she experienced a sudden loss of consciousness with tono-clonic convulsions. VF (ventricular fibrillation) was depicted on ECG. After effective resuscitation, the patient was intubated and mechanically ventilated. After restoring the sinus rhythm in ECG, the features of acute myocardial arrest with the ST-segment elevation were observed. Coronary angiography revealed occlusion of the left anterior descending coronary artery (LAD) with a thrombus and peripheral flow TIMI (Thrombin Inhibition in Myocardial Infarction) equal to 0. Hence, PTCA LAD was performed with the implantation of a metal coronary stent (resulting TIMI amounted 3). Unfortunately, the patient had some problems with circulatory and respiratory failure. In the ICU, TTM was performed (cooling to 33°C per 24 hours). On the fifth day of hospitalization the patient needed treatment with norepinephrine. During further hospitalization, gradual stabilization of markers of myocardial necrosis was observed.

The gradual return of sensorium was noted, mechanical ventilation was terminated, and passive oxygen therapy was applied. The patient was transferred to the Cardiology Department, fully alert and cooperative [55]. It seems that all of the recommended therapeutic standards were reached.



JP – Japan; IT – Italy; IN – India; DE – Germany; FR – France; CN – China; CA – Canada; BE – Belgium; AT – Austria; AU – Australia; US – United States; GB – Great Britain; TR – Turkey; TW – Taiwan; CH – Switzerland; SE – Sweden; ES – Spain; KR – Republic of Korea; NO – Norway; NL – Netherlands

Figure 1. Analysis of the frequency of PubMed entries on therapeutic hypothermia in MEDLINE (PubMed)

Total: 3,534 out of 3,661,622 entries; average interest: 0.09651%

Found in 66 out of 120 countries (55%). Development relations index (rho): 0.641

Cases of the application of TTM with therapeutic hypothermia after SCA in Polish studies

Case reports published in scientific journals offer quite valuable insight regarding implementation and the effects of TTM with therapeutic hypothermia. Gach et al. [55] described a case of a female patient (39 years old) admitted to an ICU. The patient was conscious, alert, with persistent retrosternal pain (typical of stenocar-

dia). In a study included in *Folia Cardiologica*, in turn, Kaziród-Wolski et al. [56] presented a case study of a "dramatic course of myocardial infarction in a 28-year-old patient after the use of amphetamine", where TTM was performed. Here a male patient was admitted to a hospital emergency department due to severe ret

rosteral pain persisting for several hours. After percutaneous coronary intervention (PCI), the patient was cooled with the MTH method. In the initial phase of the process, the patient's temperature decreased to 33°C (24 hours), and the pre-cooling process was initiated by an intravenous infusion of cold saline (0.9% NaCl). Later on, normothermia was systemically restored. On the fourth day, the man's reactivity improved. After five days of hospitalization, the return of effective breathing was noted (the man was extubated). Importantly, no significant deficits were found upon neurological examination. Moreover, ECG did not reveal any disturbances after three months. It seems that in this case, the use of TTM enabled the protection of the CNS from hypoxia and other negative effects [56].

In 2013, a case report by Zawiślak et al. [57] was published. It described the case of a 60-year-old patient after SCA. Myocardial infarction was diagnosed and, in connection with the persistent symptoms of cardiogenic shock and organ hypoperfusion, the patient was assumed to have an intra-aortic counter-flux, and TTM was implemented. An invasive technique was used (intravenous infusion of 0.9% NaCl solution). In further treatment, PCI was performed, and a stent implanted. After the procedure, the reduced body temperature (32–34°C) was maintained for 24 hours by cold hydrogel blankets. During the next several days of hospitalization, full hemodynamic stabilization of the patient was obtained, which made it possible to gradually reduce and then complete the catecholamine infusion. The intra-aortic counter-pulse was removed on the second day of hospitalization. On the third day, the patient was awakened and extubated. After two months, there were no adverse cardiovascular accidents, nor were there any CNS deficits noted [57].

Another case noted in a Polish scientific journal has been described by Pstrągowski [58]. The paper presents the case of a 55-year-old man after SCA. The patient experienced a sudden loss of *sensorium* preceded by chest pain. Resuscitation began at the scene of the accident, and 15 minutes later, the emergency paramedical team diagnosed VF. A paramedic performed defibrillation, and spontaneous circulation returned 20 minutes after the onset of SCA. An acute myocardial infarction with persistent ST segment elevation was detected on ECG. Coronary angiography performed in the hospital showed occlusion of the proximal section of the branch surrounding the thrombus, critical stenosis of the middle segment of the anterior interventricular branch and ruptured atherosclerotic plaque in the distal right coronary artery. Therefore, angioplasty was performed with stent implantation and thrombectomy. Simultaneously, the patient was qualified for the TTM procedure.

Before the beginning of primary coronary angioplasty, the man was covered with ice, and an intravenous infusion of saline was started. Hemodynamic stabilization was obtained (after the coronary angioplasty), and the cooling process continued via the apparatus (33–34°C) for 24 hours. The patient experienced a sudden atrial fibrillation episode. His circulation was stabilized, and he was mechanically ventilated. After the organs were in normothermia, an improvement in neurological status was found. However, deterioration of the hemodynamic condition was noted. Mechanical ventilation was maintained, and intra-aortic pumping was used, resulting in hemodynamic stabilization. On the third day, a fever (38.5°C) was noted with an increase in inflammatory parameters. Pneumonia was diagnosed. The patient experienced a drop in blood pressure with features of upper gastrointestinal bleeding. Gastroscopy and obliteration of the ruptured mucous membrane of the stomach were performed. From the fourth day of the patient's hospitalization a gradual improvement was observed, and the fever subsided (no pathogens were found in isolated material). On the sixth day, the man was disconnected from the respirator. Then, he was extubated, and intra-aortic counterpulsation was removed. During the eight-month observation period, the patient remained in a good general condition, without symptoms of heart failure and neurological disturbances.

Cases of the application of TTM with therapeutic hypothermia after SCA in other studies

In another study, Rittenberger et al. [59] presented a case of a 35-year-old woman that showed hypertension and SCA at the interview. The patient was immediately resuscitated and twice defibrillated. In the hospital, the woman was hemodynamically stabilized. In a neurological survey, 5 points were displayed (Glasgow Scale). MTH was performed via rapid infusion of 2l saline (4°C), and ice packs were implemented. Interestingly, gynaecologists confirmed the 13th week of gestation, and TTM with therapeutic hypothermia did not lead to negative consequences in the analysis of the postnatal/infant development. The woman's neurological and general condition improved after TTM. Fugate et al. [60] reported several cases. In one report, a 58-year-old patient suddenly lost consciousness, and resuscitation was necessary. Further on, the man was defibrillated. After 10–15 minutes, the cardiac rhythm was restored. Because of persistent coma, he was intubated, and MTH was initiated with a surface cooling device (target temperature 33°C, 24 h). Coronary angiography revealed occlusion of the right coronary artery (later successfully recanalized). After rewarming, the doctors had problems maintaining the patient's body temperature.

Additionally, the man presented hypertension. Two days later, he displayed the same neurological condition; he remained awake but was not cooperative. Based on the history, the doctors recognized serotonin syndrome as the patient was treated with SSRIs. In addition, the man was exposed to opioids leading to anaesthesia in the hospital.

The second case was a 36-year-old man who collapsed at home. Initially, CPR was necessary. Therapeutic hypothermia protocol was performed by the paramedics to reach the same temperature as in the first case. As a result, normothermia was disturbed. In this case, the cause was similar, that is, SSRIs combined with hospital treatment (opioids). However, over the next several days (fentanyl was excluded) the patient regained consciousness. Despite MRI not showing any alterations, the patient displayed cognitive disturbances.

In another study, Fuller et al. [61] published a case report where a 28-year-old woman was brought to the emergency department after suspected cocaine-induced cardiac arrest. The resuscitation process was performed. She recovered vital signs without the mental status improvement after defibrillation, intubation, chest compressions, and administration of emergency medicine drugs. During the next 30 minutes, the woman developed 2 more episodes of arrest, with the recovery of the signs after chest compressions, as well as epinephrine and vasopressin administrations. Later on, norepinephrine infusion was started. Because the patient's status was poor, MTH protocol was induced. Rectal temperature before initiation of active cooling was 34.7°C. The woman was further cooled to 32–33°C for 24 hours. After 48 hours, the patient presented a near-complete neurological recovery, with only mild deficits in cognitive functions.

Conclusion remarks

Primarily, it is MTH that has been considered the standard in therapeutic hypothermia. Nowadays, however, the range of body cooling protocols is wider, so TTM is more precise in terms of the description of emergency intervention with therapeutic hypothermia. When applied in patients after SCA, the method is a promising intervention, and because the evidence of its effectiveness is growing, it becomes increasingly accepted. Clinical studies indicate that the method is not only effective but also relatively safe, with many case reports showing significant benefits. Of course, every method has its disadvantages. Pstrągowski et al. [58] demonstrated both advantages and disadvantages of using therapeutic hypothermia after SCA (additionally complicated). In this case study, the hemodynamic collapse observed in the patient after the restoration of normothermia was

influenced by both the inflammatory process and hypothermia itself. It is known that lowering body temperature causes increased peripheral resistance and decreased cardiac output, which may lead to infection, as, e.g. Arrich [62] described in *Critical Care Medicine*. Currently, both ESC and the Polish Register of Therapeutic Hypothermia outline the role of this method in protecting the CNS of patients after SCA. Unfortunately, TTM (despite the observed relatively positive trend of increasing popularity and implementation) has not been widely used and made obligatory in recent years in Poland. Barriers to guideline implementation include lack of knowledge and experience, and lack of reimbursement of costs for this therapy, as Krawczyk [50] has already described. In confirming the lack of medical personnel's knowledge and relatively low use of TTM in Poland, this work brings awareness to a potentially significant lapse in patient care after SCA. The recent study by Kowalik et al. [63] of 2020 seems promising. The authors show that recently Intensive Cardiac Care Units have increasingly implemented this method of emergency. Our analysis of MTH, particularly TTM, in Poland compared to other countries should be assumed by Seth Godin's business sentence: *"The cost of being wrong is less than the cost of doing nothing"*. Emergency medicine is a very sensitive branch of medicine. However, based on the research and experts' opinions, we should implement the latest solutions in order to rescue health and life.

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