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The prognostic impact of therapeutic hypothermia after a sudden cardiac arrest in the course of myocardial infarction

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Abstract

Background: *Mild therapeutic hypothermia (MTH) is one of the treatment methods recommended in post-sudden cardiac arrest (SCA) patients who remain unconscious after cardiopulmonary resuscitation. The present study aimed at assessing the prognostic impact of intravascular MTH on invasively treated patients with an acute myocardial infarction complicated by SCA.*

Methods: *The presented data were collected via a single-center retrospective analysis of the hospitalization and follow-up of 54 patients with post-myocardial infarction complicated by SCA. The patients were treated in the years 2014–2020 and the average follow-up period was 1141 ± 163 days. The population was divided into two groups: 28 patients treated with MTH (a therapeutic hypothermia [TH] group) and 26 patients treated without MTH (a non-TH group).*

Results: *The results indicate a trend toward improved in-hospital prognosis in the TH group, but the differences did not reach statistical significance: TH 25.0% vs. non-TH 34.5%, p = 0.554. An additional analysis of younger patients (under 60 years of age) revealed no significant differences between the TH and non-TH subgroups concerning in-hospital survival (in-hospital mortality rate: TH 6.7% vs. non-TH 30.0%, p = 0.267). Still, TH patients aged < 60 achieved a significantly better rate of follow-up survival (p = 0.041). The older (≥ 60) patient group showed no in-hospital mortality rate differences (TH 46.2% vs. non-TH 37.5%, p = 0.638). However, in-hospital bleeding frequency was significantly higher in patients aged ≥ 60 from the hypothermia group (TH 50.0% vs. non-TH 6.7%, p = 0.011).*

Conclusions: *Intravascular MTH may improve the follow-up prognosis in patients aged < 60 with SCA in the early phase of myocardial infarction.* (Cardiol J)

Key words: therapeutic hypothermia, myocardial infarction, cardiac arrest, target temperature management

Introduction

According to the European Resuscitation Council (ERC) 2021 guidelines, the annual frequency of out-of-hospital cardiac arrest (OHCA) in Europe is 67–170 per 100,000 residents, while in-hospital cardiac arrest (IHCA) occurs in 1.5–2.8 per 1000 patients annually [1]. The most frequent causes of cardiac arrest include acute coronary syndromes. The current ERC guidelines for patients

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after a sudden cardiac arrest (SCA) who remain unconscious following the return of spontaneous circulation recommend targeted temperature management, which consists in maintaining constant temperature of 32–36°C for at least 24 hours and avoiding fever (a temperature of > 37.7°C) for at least 72 hours.

The Polish Registry of Therapeutic Hypothermia obtained data on 377 patients with OHCA from 26 centers and showed the intensive cardiac care units (ICCU) has become a valuable alternative to the intensive care unit (ICU) to provide treatment for patients with OHCA with similar survival rates and neurologic outcome, with a high percentage of good results and an acceptable level of poor outcomes, were observed both for the ICCU and ICU [2].

Therapeutic hypothermia in post-SCA patients reduces inflammatory response and apoptosis related to post-cardiac arrest syndrome. The latter consists of hypoxic brain injury, circulatory system dysfunction and complications stemming from tissue ischemia and reperfusion [3]. Moreover, the leading cause of premature deaths in approximately 23% of patients after an in-hospital SCA is post-cardiac arrest shock [4].

Hypothermia after Cardiac Arrest Study Group [5] proved already in 2002 that mild hypothermia (32–34°C) improved the neurological status and reduced the total mortality rate among patients who developed an SCA in the course of ventricular fibrillation and then achieved return of spontaneous circulation. The clinical trials that followed confirmed that mild hypothermia improved the neurological status of post-SCA patients [6–9]. Moreover, therapeutic hypothermia (TH) might result in better survival rates among patients with a shockable baseline rhythm [10].

The preclinical studies conducted by Kern et al. [11] highlight that quick reperfusion via coronary angioplasty and TH are both important in limiting the myocardial infarct size.

The main methods of hypothermia induction and maintenance are: surface cooling and intravascular (invasive) cooling. A meta-analysis comparing those two methods did not determine differences in the time passing from SCA onset to target temperature achievement. However, it showed that patients from the intravascular cooling group required shorter hospitalization and shorter stays in ICUs as well as having better neurological prognoses in comparison with patients from the surface cooling group [12].

The study aimed at determining the impact of intravascular hypothermia on the follow-up prognosis for patients post-SCA in the early phase of myocardial infarction (MI) as well as assessing the results in relation to old age (≥ 60 years). It also included an additional analysis of in-hospital complications and neurological status at discharge, the latter assessed using the Glasgow-Pittsburgh Cerebral Performance Categories (CPC).

Methods

The intravascular hypothermia protocol

The study included unconscious patients admitted to hospital after effective cardiopulmonary resuscitation performed due to an SCA in the course of an acute MI who were treated using intravascular mild therapeutic hypothermia (MTH). Hypothermia was managed according to an established protocol which consisted of four phases: cooling, temperature maintenance, slow rewarming and fever control. The cooling phase was commenced as soon as it was possible via intravenous administration of saline cooled down to 4°C as well as using the Thermogard XP Temperature Management System — an intravascular hypothermia system by ZOLL. The core temperature achieved at the end of the cooling phase reached 32.5 ± 0.1°C as measured using a thermistor-based esophageal probe. The target temperature for patients with a cardiogenic shock upon admission was 35 ± 0.2°C. The subsequent target temperature maintenance phase lasted 24 hours. Then the patients were slowly rewarmed to a temperature of 36.5°C at a pace of 0.1°C per hour. Finally, they underwent the fever control phase during which the maximal core temperature was 36.6°C. Sedation and mechanical ventilation was applied in all patients. Muscle relaxants were administered as well to prevent convulsions.

Data acquisition

The study was based on a single-center retrospective and prospective analysis of data concerning patients who developed an SCA in the course of acute MI and were hospitalized in the years 2014–2020. The patient survival data were collected based on the medical records of outpatient visits and via telephone conversations with patients or their families. The minimal period of follow-up was 340 days (on average: 1141 ± 163 days).

Ninety-eight patients diagnosed with an SCA were treated in the years 2014–2020. The analysis

excluded patients who: did not have a MI, were aged ≥ 75 years, had a diagnosis of a neoplastic disease, had died before coronarography or scored ≥ 8 points on the Glasgow Coma Scale (GCS). Thus, the analysis eventually included 54 patients divided into two groups: patients treated with mild intravascular hypothermia (n = 28) and patients treated without using mild intravascular hypothermia (n = 26). An additional analysis concerned subgroups of patients aged ≥ 60 years and < 60 years.

The log of patients with a MI complicated by SCA who were treated in the Silesian Center for Heart Diseases (SCCS) using MTH was submitted to the Bioethics Committee of the Medical University of Silesia (SUM) for approval. Due to the retrospective nature of the log, the abovementioned approval is not required. The data were collected in line with the commonly binding provisions of law, including personal data protection requirements, patient rights and principles of using human biological material.

Statistical analysis

Qualitative variables are reported as percentage. Quantitative variables are reported as mean with standard deviation or as median with the lower and upper quartiles. The goodness of fit for the distribution of quantitative variables was assessed using the Shapiro-Wilk test. Quantitative variables were analyzed using Student's t-test or the Mann-Whitney U test depending on the distribution. Qualitative variables were compared using the χ^2 test or the Fisher exact test.

The follow-up survival was assessed via the Kaplan-Meier estimator and the generated survival curves were compared using the log-rank test. The statistical analyzes were performed with the SPSS Statistics software by IBM (ver. 28.0).

Results

The 54 studied patients were divided into two groups: 28 patients treated with MTH (a TH group) and 26 patients treated without MTH (a non-TH group). The groups did not differ in terms of demographic features such as sex, age or medical history (including arterial hypertension, diabetes mellitus and coronary artery disease) (Table 1). The majority of the studied population (70.4%) was patients with OHCA. OHCA occurred in 61.5% of patients not treated with hypothermia and 78.6% of patients treated with hypothermia (p = 0.236). In most patients (86.8%) SCA occurred with a shockable rhythm. There were 88.5% of patients with a shockable rhythm in the non-TH group and 85.2% in the TH group (p = 1.000). The highest percentage of patients (40.7%) had an anterior wall ST-segment elevation MI. The two analyzed groups did not differ in terms of MI location. Cardiogenic shock upon admission was diagnosed in 34.0% of patients (46.2% in the non-TH group and 22.2% in the TH group, p = 0.086).

All patients underwent standard management of MI according to the European Society of Cardiology 2015 guidelines, including invasive diagnostics of coronary arteries and coronary angioplasty. The infarct-related artery (IRA) patency was restored in 90.4% of all patients, including 96.2% of non-TH patients and 84.6% of TH patients (p = 0.35) (Table 2).

No statistically significant differences were determined between the TH group and the non-TH group in terms of the following parameters upon admission: hematocrit (non-TH: 40.8% [interquartile range, IR: 38.6–46.2%], TH: 41.9% [IR: 37.9–45.8%], p = 0.533), platelets (235×103/μL [IR: 172–289×103/μL] vs. 271×103/μL [IR: 215–324×103/μL], p = 0.709) and white blood cells (16.46×103/μL [IR: 11.6–21.9×103/μL] vs. 16.49×103/μL [IR: 13.71–19.91×103/μL], p = 0.930). The blood lactate levels upon admission did not show statistically significant differences either (non-TH: 7.42 mmol/L [IR: 4.77–9.2 mmol/L] vs. TH: 6.0 mmol/L [IR: 4.5–7.73 mmol/L], p = 0.496). However, the non-TH group had statistically significant higher levels of creatinine (124 mmol/L [IR: 106–176 mmol/L] vs. 110 mmol/L [IR: 96–136 mmol/L], p = 0.03) and C-reactive protein (7.64 mg/dL [IR: 3.16–47.11 mg/dL] vs. 3.33 mg/dL [IR: 1.16–5.05 mg/dL], p = 0.022).

In-hospital infections were equally common in both groups, but sepsis was statistically more frequent in the non-TH group (24% vs. 3.7%, p = 0.046). Other infections, such as pneumonia and urinary tract infections, were equally frequent in both patient groups. Similarly, no frequency differences were determined for in-hospital complications such as contrast-induced nephropathy (CIN) (non-TH: 12.0% vs. TH: 7.4%, p = 0.662), dialysis (non-TH: 8.0% vs. TH: 7.4%, p = 1), bleeding (non-TH: 12.0% vs. TH: 29.6%, p = 0.177), stent thrombosis (non-TH: 3.8% vs. TH: 0%, p = 0.491), thrombocytosis (non-TH: 0% vs. TH: 17.9%, p = 0.052) and de novo atrial fibrillation (AF) (non-TH: 15.4% vs. TH: 10.7%, p = 0.699).

In-hospital death occurred in 29.6% of admitted patients, including in 13.0% of patients within 24 hours of admission. The groups did not differ in

Table 1. Characterization of the analyzed patient groups.

	All patients (n = 54)	Non-TH group (n = 26)	TH group (n = 28)	P	All patients aged < 60 years (n = 25)	Non-TH group aged < 60 years (n = 10)	TH group aged < 60 years (n = 15)	P	All patients aged ≥ 60 years (n = 29)	Non-TH group aged ≥ 60 years (n = 16)	TH group aged ≥ 60 years (n = 13)	P
Mean age [years], SD, Me, IR	59 ± 8	61 ± 6	58 ± 9	0.106	54 (IR: 48–58)	56 (IR: 52–58)	49 (IR: 47–58)	0.144	64 (IR: 61–68)	65 (IR: 62–68)	64 (IR: 61–68)	0.948
Sex: male	42 (77.8%)	20 (76.9%)	22 (78.6%)	1.000	19 (76%)	8 (80%)	11 (73.3%)	1.000	23 (79.3%)	12 (75%)	11 (84.6%)	0.525
History:												
Arterial hypertension	34 (66.7%)	18 (75%)	16 (59.3%)	0.372	13 (56.5%)	5 (55.6%)	8 (57.1%)	1.000	21 (75%)	13 (86.7%)	8 (61.5%)	0.126
Diabetes mellitus	16 (30.8%)	9 (37.5%)	7 (25%)	0.378	5 (20.8%)	2 (22.2%)	3 (20%)	1.000	11 (39.3%)	7 (46.7%)	4 (30.8%)	0.390
Past coronary disease	21 (38.9%)	11 (42.3%)	10 (35.7%)	0.781	5 (20%)	2 (20%)	3 (20%)	1.000	16 (55.2%)	9 (56.3%)	7 (53.8%)	0.897
Sudden cardiac arrest:												0.948
Out-of-hospital	38 (70.4%)	16 (61.5%)	22 (78.6%)	0.236	21 (84%)	8 (80%)	13 (86.7%)	1.000	17 (58.6%)	8 (50%)	9 (69.2%)	0.296
Shockable rhythm	46 (86.8%)	23 (88.5%)	23 (85.2%)	1.000	22 (91.7%)	9 (90%)	13 (92.9%)	1.000	24 (82.8%)	14 (87.5%)	10 (76.9%)	0.453
Shock upon admission	18 (34%)	12 (46.2%)	6 (22.2%)	0.086	8 (33.3%)	4 (40%)	4 (28.6%)	0.673	10 (34.5%)	8 (50%)	2 (15.4%)	0.051
Anterior wall STEMI	22 (40.7%)	12 (46.2%)	10 (35.7%)	0.580	14 (56%)	7 (70%)	7 (46.7%)	0.414	8 (27.6%)	5 (31.3%)	3 (23.1%)	0.624
Inferior wall STEMI	17 (31.5%)	5 (19.2%)	12 (42.9%)	0.082	8 (32%)	2 (20%)	6 (40%)	0.402	9 (31%)	3 (18.8%)	6 (46.2%)	0.113
STEMI in other locations	3 (5.6%)	2 (7.7%)	1 (3.6%)	0.604	1 (4%)	1 (10%)	0 (0%)	0.400	2 (6.9%)	1 (6.3%)	1 (7.7%)	0.879
NSTEMI	12 (22.2%)	7 (26.9%)	5 (17.9%)	0.520	2 (8%)	0 (0%)	2 (13.3%)	0.500	10 (34.5%)	7 (43.8%)	3 (23.1%)	0.244
LVEF [%], Me, IR	37 (IR: 28–45)	36 (IR: 21–40)	40 (IR: 30–45)	0.149	40 (32; 45)	40 (34; 45)	41 (32; 46)	0.714	35 (IR: 20–40)	29 (IR: 20–39)	35 (IR: 30–45)	0.235
Admission HCT [%], Me, IR	41.5 (IR: 38.3–45.9)	40.8 (IR: 38.6–46.2)	41.9 (IR: 37.9–45.8)	0.533	42.2 (IR: 39.6–46.2)	44.3 (IR: 41.6–48.8)	41 (IR: 38–44.2)	0.177	41.6 (IR: 38.7–45.8)	40.4 (IR: 39–44.7)	43.6 (IR: 37.4–46.1)	0.728
Admission PLT [$10^3/\mu$L], Me, IR	248 (IR: 193–292)	235 (IR: 172–289)	271 (IR: 215–324)	0.709	264 (IR: 225– 308)	265 (IR: 248–292)	257 (IR: 215–324)	0.709	238 (IR: 180–290)	209 (IR: 172–256)	277 (IR: 225–324)	0.152
Admission WBC [$10^3/\mu$L], Me, IR	16.49 (IR: 12.88–21.12)	16.46 (IR: 11.6–21.9)	16.49 (IR: 13.71–19.91)	0.930	18.5 (IR: 14.64–23.4)	21.21 (IR: 14.64–24.41)	18.17 (IR: 13.48–23.04)	0.495	15.61 (IR: 12.57–18.81)	16 (IR: 11.6–18.81)	15.53 (IR: 13.71–18.13)	0.650
Admission potassium [mmol/L], Me, IR	4.38 (IR: 3.91–5.04)	4.43 (IR: 3.96–5.12)	4.24 (IR: 3.78–4.79)	1.000	4.24 (IR: 3.69–4.48)	4.24 (IR: 3.68–4.48)	4.24 (IR: 3.69–4.6)	1.000	4.49 (IR: 3.91–5.23)	4.58 (IR: 4.1–5.25)	4.38 (IR: 3.79–5.06)	0.503
Admission CK-MB [ng/mL], Me, IR	18.52 (IR: 6.25–47.95)	20.44 (IR: 7.56–64.78)	16.99 (IR: 5.3–32.91)	0.137	16.99 (IR: 7.56–34.93)	30.43 (IR: 11.35–125.7)	10.29 (IR: 3.97–28)	0.036*	19.2 (IR: 6.57–59.6)	13.91 (IR: 6.57–64.35)	19.95 (IR: 8.3–34.06)	1.000
Admission creatinine [mmol/L], Me, IR	117 (IR: 100–150)	124 (IR: 106–176)	110 (IR: 96–136)	0.030*	113 (IR: 96–124)	119 (IR: 106–146)	105 (IR: 86–121)	0.144	132 (IR: 104–174)	148 (IR: 107–188)	110 (IR: 98–150)	0.249
Admission CRP [mg/dL], Me, IR	4.24 (IR: 1.8–19.95)	7.64 (IR: 3.16–47.11)	3.33 (IR: 1.16–5.05)	0.022*	3.36 (IR: 0.9–6.85)	6.81 (IR: 3.78–33.96)	1.66 (IR: 0.77–4.85)	0.091	4.47 (IR: 3.33–17.35)	6.91 (IR: 3.52–22.61)	4.24 (IR: 3.33–6.07)	0.423
Admission lactates [mmol/L], Me, IR	6.12 (IR: 4.5–9)	7.42 (IR: 4.77–9.2)	6 (IR: 4.5–7.73)	0.496	6.07 (IR: 5.02–7.77)	5.54 (IR: 3.66–6.71)	7 (IR: 5.75–9.8)	0.115	7.24 (IR: 3.8–9.2)	8.92 (IR: 7.25–9.3)	4.65 (IR: 3.8–6.1)	0.07

*p < 0.05; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction, LVEF — left ventricular ejection fraction, CK-MB — cardiac isoenzyme of creatine kinase (CK-MB mass); CRP — C-reactive protein; SD — standard deviation; Me — median; IR — interquartile range; PLT — platelet; HCT — hematocrit; WBC — white blood cells

Table 2. Hospital course in the analyzed groups.

	All patients (n = 54)	Non-TH group (n = 26)	TH group (n = 28)	P	All patients aged < 60 years (n = 25)	Non-TH group aged < 60 years (n = 10)	TH group aged < 60 years (n = 15)	P	All patients aged ≥ 60 years (n = 29)	Non-TH group aged ≥ 60 years (n = 16)	TH group aged ≥ 60 years (n = 10)	P
Treatment:												
IABP	17 (32.1%)	11 (42.3%)	6 (22.2%)	0.117	9 (36%)	4 (40%)	5 (33.3%)	1.000	8 (28.6%)	7 (43.8%)	1 (8.3%)	0.040*
ECMO	2 (3.7%)	1 (3.8%)	1 (3.6%)	1.000	2 (8%)	1 (10%)	1 (6.7%)	1.000	0 (0%)	0 (0%)	0 (0%)	–
IRA patency restoration	47 (90.4%)	25 (96.2%)	22 (84.6%)	0.350	23 (95.8%)	10 (100%)	13 (92.9%)	1.000	24 (85.7%)	15 (93.8%)	9 (75%)	0.161
Clopidogrel	13 (27.1%)	7 (31.8%)	6 (23.1%)	0.532	4 (16.7%)	1 (10%)	3 (21.4%)	0.615	9 (36%)	6 (46.2%)	3 (25%)	0.271
Ticagrelor	32 (65.3%)	14 (60.9%)	18 (69.2%)	0.564	17 (70.8%)	8 (80%)	9 (64.3%)	0.653	15 (60%)	6 (46.2%)	9 (75%)	0.141
Prasugrel	2 (3.8%)	0 (0%)	2 (7.4%)	0.491	1 (4.2%)	0 (0%)	1 (7.1%)	1.000	1 (3.4%)	0 (0%)	1 (7.7%)	0.259
Noradrenaline	29 (59.2%)	16 (69.6%)	13 (50%)	0.245	15 (62.5%)	7 (70%)	8 (57.1%)	0.678	14 (56%)	9 (69.2%)	5 (41.7%)	0.165
Dobutamine	27 (55.1%)	15 (65.2%)	12 (46.2%)	0.252	14 (58.3%)	7 (70%)	7 (50%)	0.421	13 (52%)	8 (61.5%)	5 (41.7%)	0.320
Insulin	27 (55.1%)	13 (56.5%)	14 (53.8%)	1.000	11 (45.8%)	4 (40%)	7 (50%)	0.697	16 (64%)	9 (69.2%)	7 (58.3%)	0.571
Complications:												
Infections	31 (57.4%)	15 (57.7%)	16 (57.1%)	1.000	15 (60%)	5 (50%)	10 (66.7%)	0.678	16 (55.2%)	10 (62.5%)	6 (46.2%)	0.379
Sepsis	7 (13.5%)	6 (24%)	1 (3.7%)	0.046*	2 (8%)	2 (20%)	0 (0%)	0.150	5 (18.5%)	4 (26.7%)	1 (8.3%)	0.223
Lower respiratory tract infection	25 (48.1%)	10 (40%)	15 (55.6%)	0.283	14 (56%)	3 (30%)	11 (73.3%)	0.049*	11 (40.7%)	7 (46.7%)	4 (33.3%)	0.484
Urinary tract infection	8 (15.7%)	4 (16%)	4 (15.4%)	1.000	3 (12%)	1 (10%)	2 (13.3%)	1.000	6 (22.2%)	3 (20%)	3 (25%)	0.756
CIN	5 (9.6%)	3 (12%)	2 (7.4%)	0.662	1 (4%)	1 (10%)	0 (0%)	0.400	4 (14.8%)	2 (13.3%)	2 (16.7%)	0.809
Dialysis	4 (7.7%)	2 (8%)	2 (7.4%)	1.000	1 (4%)	1 (10%)	0 (0%)	0.400	3 (11.1%)	1 (6.7%)	2 (16.7%)	0.411
Bleeding	11 (21.2%)	3 (12%)	8 (29.6%)	0.177	4 (16%)	2 (20%)	2 (13.3%)	1.000	7 (25.9%)	1 (6.7%)	6 (50%)	0.011*
Blood transfusion	22 (40.7%)	12 (46.2%)	10 (35.7%)	0.580	9 (36%)	5 (50%)	4 (26.7%)	0.397	13 (44.8%)	7 (43.8%)	6 (46.2%)	0.897
De novo AF	7 (13.0%)	4 (15.4%)	3 (10.7%)	0.699	3 (12%)	1 (10%)	2 (13.3%)	1.000	4 (13.8%)	3 (18.8%)	1 (7.7%)	0.390
Coagulation disorders	7 (13.2%)	2 (7.7%)	5 (18.5%)	0.420	4 (16%)	1 (10%)	3 (20%)	0.626	3 (10.3%)	1 (6.3%)	2 (15.4%)	0.422
In-hospital thrombocytosis	5 (9.3%)	0 (0%)	5 (17.9%)	0.052	4 (16%)	0 (0%)	4 (26.7%)	0.125	1 (3.4%)	0 (0%)	1 (7.7%)	0.259
Stent thrombosis	1 (1.9%)	1 (3.8%)	0 (0%)	0.491	1 (4%)	1 (10%)	0 (0%)	0.400	0 (0%)	0 (0%)	0 (0%)	–
In-hospital death	16 (29.6%)	9 (34.6%)	7 (25.0%)	0.554	4 (16%)	3 (30%)	1 (6.7%)	0.267	12 (41.4%)	6 (37.5%)	6 (46.2%)	0.638
Death within 24 h	7 (13%)	5 (19.2%)	2 (7.1%)	0.186	2 (8%)	1 (10%)	1 (6.7%)	1.000	5 (17.2%)	4 (25%)	1 (7.7%)	0.220
CPC 1–2	19 (35.2%)	9 (34.6%)	10 (35.7%)	1.000	12 (48%)	4 (40%)	8 (53.3%)	0.688	7 (24.1%)	5 (31.3%)	2 (15.4%)	0.321
CPC 3–5	35 (64.8%)	17 (65.4%)	18 (64.3%)	1.000	13 (52%)	6 (60%)	7 (46.7%)	0.688	22 (75.9%)	11 (68.8%)	11 (84.6%)	0.321

*$p < 0.05$; IABP — intra-aortic balloon pump; ECMO — extracorporeal membrane oxygenation; IRA — infarct-related artery; CIN — contrast-induced nephropathy; AF — atrial fibrillation; CPC — Glasgow-Pittsburgh Cerebral Performance Categorie

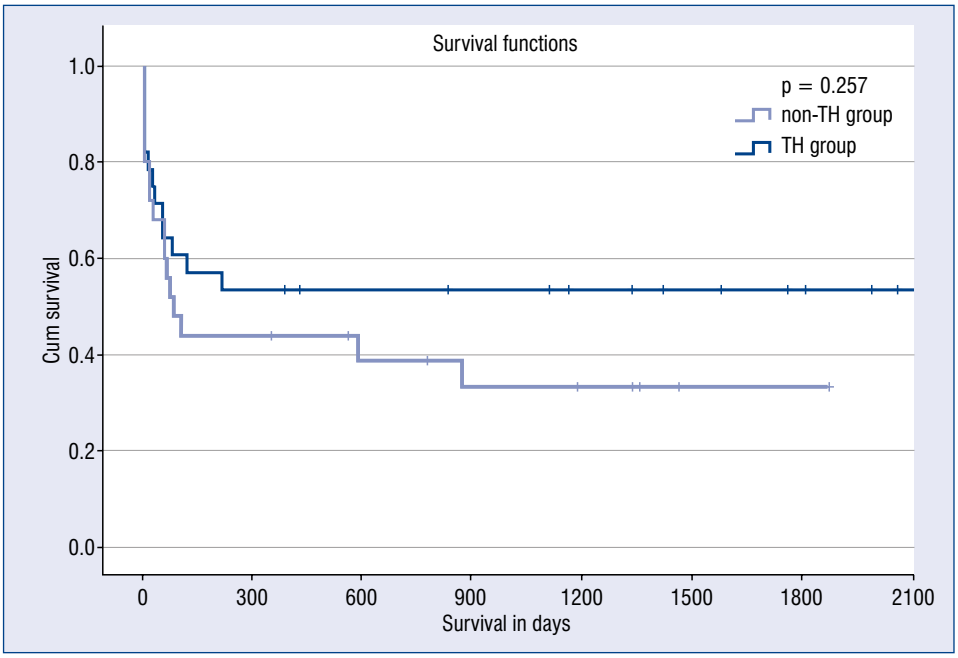

Figure 1. Comparison of survival curves of the therapeutic hypothermia (TH) and non-TH groups.

terms of in-hospital survival (non-TH: 19.2% vs. TH: 7.1%, p = 0.554) or first-day survival (non--TH: 19.2% vs. 7.1%, p = 0.186). The neurological status at discharge was assessed as bad (CPC 3–5) in 64.8% of patients (non-TH: 65.4%, TH: 64.3%, p = 1.000), which included vegetative state and in-hospital death. Good neurological status (CPC 1–2) was achieved in 34.6% of non-TH patients and 35.7% of TH patients (p = 1.000).

An analysis of follow-up survival (average follow-up period: 1141 ± 163 days) showed slightly better survival trends in the TH group, but the differences between the Kaplan-Meier curves for both groups were not statistically significant (p = 0.257; Fig. 1).

Regarding the subgroup aged < 60 years (n = 25), 15 patients were treated with MTH, while 10 underwent treatment without hypothermia. In the subgroup aged ≥ 60 years (n = 29), those numbers were 13 and 16, respectively.

The analyzed subgroups of younger and older patients did not differ in terms of sex, age distribution or medical history (including arterial hypertension, type 2 diabetes mellitus and coronary artery disease).

No statistically significant differences were determined concerning SCA mechanism or location in the analyzed subgroups of younger and older patients. SCA with shockable rhythm and out-of-hospital SCA (OHCA) dominated in both subgroups. Non-ST-segment elevation MI prevailed in the ≥ 60 subgroup (34.5%), while its frequency in the < 60 group was 8%.

Laboratory tests performed upon admission in the group of patients aged < 60 revealed significantly higher levels of the cardiac isoenzyme of creatine kinase (CK-MB mass) in the non-TH subgroup (30.43 ng/mL; 11.35–125.7 ng/mL vs. 10.29 ng/mL; 3.97–28.0 ng/mL, p = 0.036). No significant differences in terms of CBC parameters were observed between the analyzed subgroups. Similarly, the group of patients aged ≥ 60 did not show statistically significant differences in biochemical parameters depending on MTH application.

The analyzed subgroups of patients aged < 60 did not demonstrate differences regarding in-hospital complications such as CIN (non-TH: 10.0% vs. TH: 0%, p = 0.400), coagulation disorders (non-TH: 10.0% vs. TH: 20.0%, p = 0.626), bleeding (non-TH: 20.0% vs. TH 13.3%, p = 1.000) or de novo AF (non-TH: 10.0% vs. TH: 13.3%, p = 1.000). The frequency of bleeding was statistically significantly higher in patients aged ≥ 60 provided that MTH was applied (50.0% vs. 6.7%, p = 0.011). However, it did not entail a higher frequency of blood transfusions (non-TH: 43.8% vs. TH: 46.2%, p = 0.897). No statistically significant differences were determined among the ≥ 60 patients in terms of complications such as CIN or dialysis (non-TH: 13.3% vs. TH: 16.7%, p = 0.809, and 6.7% vs.

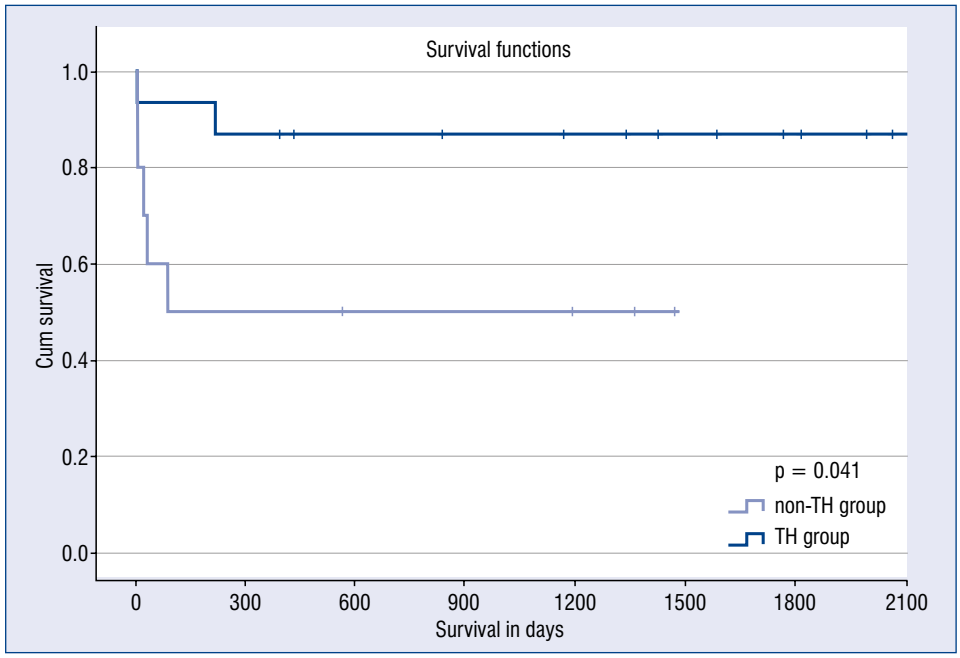

Figure 2. Survival curves in the group of patients aged < 60 years depending on the application of therapeutic hypothermia (TH).

16.7%, p = 0.411). Abnormal heart rhythm in the form of de novo AF occurred in 13.8% of the older patient group, without differences between the non-TH and TH subgroups (18.8% vs. 7.7%, p = 0.259).

The two subgroups of patients aged < 60 showed a similar frequency of in-hospital infections regardless of MTH application (non-TH: 50.0% vs. TH: 66.7%, p = 0.678). However, the frequency of pneumonia was significantly higher in the MTH group (73.3% vs. 30.0%, p = 0.049). Urinary tract infections and septic complications did not demonstrate such frequency differences though. The group of patients aged ≥ 60 did not differ in terms of infection frequency depending on MTH application (TH: 62.5% vs. non-TH: 46.2%, p = 0.379).

In-hospital death occurred in 16.0% of patients aged < 60 and 41.1% of patients aged ≥ 60. No impact of MTH on the in-hospital mortality rate was determined in the age groups. Mortality before discharge among patients aged < 60 reached 30.0% in the non-MTH subgroup and 6.7% in the MTH subgroup (p = 0.267). In the group of patients aged ≥ 60, those values equaled 37.5% and 46.2%, respectively (p = 0.638). No differences were determined between first-day survival rates.

The CPC neurological status at discharge did not differ between younger and older patients and did not depend on MTH application.

Mild TH significantly improved the follow-up prognosis among patients aged < 60. Figure 2 shows the survival curves for the analyzed subgroup. However, no favorable impact of MTH on the follow-up prognosis was seen among patients aged ≥ 60.

Discussion

The results of a multicenter randomized study involving 275 patients published in 2002 proved that MTH (32–34°C) in patients post-SCA with ventricular fibrillation entailed a better neurological prognosis and reduced mortality [5]. The European Society of Cardiology 2015 guidelines on ventricular arrhythmias mention TH as an element of multidisciplinary treatment in the centers where one should refer patients post-SCA associated with acute coronary syndromes [13]. Moreover, the HYPERION (Therapeutic Hypothermia after Cardiac Arrest in Non-shockable Rhythm) randomized trial proved that MTH of 33°C in patients post-SCA with a non-shockable rhythm improved the outcome of a neurological assessment carried out in the 90th day of the follow-up [14].

Other authors have not confirmed the beneficial effects of MTH in patients after SCA in published papers. In a systemic review and meta-analysis published by Granfeldt et al. [15] among adult patients with cardiac arrest, the use of tar-

geted temperature management at 32–34°C, when compared to normothermia, did not result in improved survival or neurologic outcome at 90 to 180 days after cardiac arrest.

Results of preclinical studies concerning MTH confirmed its effectiveness in limiting the myocardial infarct size provided that hypothermia was commenced before the reperfusion phase [11, 16, 17]. Even though the abovementioned results have not been confirmed by clinical trials yet, they did demonstrate the safety of intravascular hypothermia in patients with an MI [18–20].

Similarly, the studied population of patients did not show significant differences in the frequency of in-hospital complications. Only septic state confirmed by positive culture results occurred more frequently in the non-MTH group, which may have been caused by administering antibiotic therapy from the beginning of hospitalization in patients undergoing TH and by the higher levels of C-reactive protein upon admission in non-MTH patients. The results of the trial published by Dankiewicz et al. [21], which included 939 post-SCA patients either treated or not treated with hypothermia (33°C and 36°C, respectively), also failed to prove a statistically significant difference in the number of infectious complications. Pneumonia was significantly more frequent (73.3%) in the group of patients aged < 60 years who underwent TH. However, it did not impact the in-hospital mortality rate. A meta-analysis performed by Xiao et al. [22] showed a tendency toward more frequent pneumonia in the group of TH-treated patients, but without statistical significance. Another meta-analysis, performed by Geurts et al. [23], demonstrated a higher risk of sepsis and pneumonia in the group of patients undergoing TH, but no differences were proved after taking all infections into account.

Papers on TH in post-SCA patients highlight a higher frequency of de novo AF in patients undergoing TH [20, 24]. However, AF occurrence has not been proved to worsen the prognosis. The present study did not confirm differences in the frequency of de novo AF in relation to MTH.

It stems from previous papers that old age is one of the main factors which negatively affect the prognosis of patients with an MI who develop an SCA [25, 26]. However, the benefits of MTH depending on patient age were not analyzed. The patient group in the present analysis was relatively small, so we divided it into only two subgroups (patients aged < 60 and patients aged ≥ 60). A favorable impact of MTH was proved on the prognosis of younger patients, but the group aged ≥ 60 did not show a similarly beneficial relationship. The obtained results are related to the frequency of bleeding complications. The bleeding frequency in the studied population was high, reaching 21.2% regardless of MTH. A similarly high percentage of bleeding complications in the population of patients with SCA in the course of MI had been determined in previous studies as well [27]. An interpretation of the obtained results allows a statement that the lack of a favorable MTH impact on patients aged ≥ 60 might have been caused by the higher bleeding frequency (25.9%) in that group in comparison with younger patients (16%).

Koren et al. [28] highlight the need to take the age and the SCA-inducing arrhythmia into account when qualifying patients for TH. The present study proves the importance of appropriate qualification of patients for MTH. The group of patients suffering an SCA during MI who benefit from TH regardless of the SCA-inducing arrhythmia is patients aged < 60 years.

To predict in-hospital mortality in OHCA patients treated with targeted temperature management, the Polish Hypothermia Registry Risk Score (PHR-RS) was developed. The PHR-RS was created based on the multicenter register and includes age and MTH score. The use of dedicated risk stratification tools may support treatment decisions [29].

Limitations, strength of the study and perspectives

The study is limited by its retrospective nature. Moreover, the presented results come from a single center. The studied group was small and the applied MTH protocol might have influenced the conclusions as well. The strength of the present study is the homogeneous protocol of MTH and the same cooling machine was used within treated patients with MTH. Other studies have presented divergent results concerning survival and neurological status assessment of post-SCA patients depending on the obtained target temperature (between 33°C and 36°C) and fever control (i.e., avoiding the temperature of > 37.7°C [30, 31]). It remains unclear whether following a different MTH protocol in patients aged ≥ 60 years would have resulted in greater benefits, including reducing the frequency of bleeding complications. Further studies and randomized trials, using homogeneous cooling methodology and protocols, especially on the impact of MTH on neurological status after SCA are needed.

Conclusions

Intravascular MTH applied in patients who suffer an SCA in the early phase of an MI may improve the follow-up prognosis of patients aged < 60 years but does not affect the prognosis of those aged ≥ 60. Moreover, TH in patients aged ≥ 60 may increase the bleeding risk. Therapeutic hypothermia does not impact the neurological status at discharge. Thus, a patients' age is a factor to consider when qualifying them for treatment with the use of intravascular therapeutic hypothermia.

Conflict of interest: Andrzej Świątkowski and Jacek Kowalczyk — Investigators of COOL-AMI EU trials; Beata Średniawa — Consultancy fee for ZOLL Medical during COOL-AMI EU trials as an Principal Investigator for Poland and a member of Advisory Board. All other authors declare no conflict of interest.

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