Therapeutic hypothermia after cardiac arrest in a real-life setting

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ABSTRACT

INTRODUCTION: In 2002, two landmark studies concluded that therapeutic hypothermia (TH) improves survival and neurologic outcome in patients with shockable rhythms and out-of-hospital cardiac arrest (OHCA). However, the evidence on whether TH also improves the prognosis in patients with non-shockable rhythms or in-hospital cardiac arrest (IHCA) is sparse. The aim of this study was to assess the prevalence and prognosis of patients with non-shockable rhythms or IHCA after implementation of TH in a real-life setting.

METHODS: The study included 72 consecutive, unconscious patients that were admitted to Holbaek Hospital after cardiac arrest and successful resuscitation. Patients were included regardless of initial cardiac rhythms and location of the cardiac arrest. All patients were cooled to a temperature of 32-34 °C. The primary outcome was survival with a favourable neurologic outcome within six months.

RESULTS: Almost two thirds (63%) of the included patients had non-shockable rhythms or IHCA and only 8.7% of these patients survived with a favourable neurologic outcome. Nearly a third (29%) of the included patients had OHCA with an initial non-shockable rhythm and none (0%) of these patients survived with a favourable neurologic outcome.

CONCLUSIONS: In a real life setting, the majority of resuscitated patients receiving TH do not fulfil the criteria of the original studies upon which the current guidelines are based. Furthermore, these patients have a poor outcome, indicating that not all patients may benefit from TH.

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In 2002, two randomised clinical trials (RCT) were published [1, 2]. In these trials, patients with out-of-hospital cardiac arrest (OHCA) and shockable rhythms (ventricular fibrillation (VF) or ventricular tackycardia (VT)) who remained comatose after resuscitation were randomised to therapeutic hypothermia (TH) (32-34 °C) or standard treatment. In conclusion, these trials showed an improved neurological outcome and a reduced mortality in patients receiving TH. Based on these results, the International Committee On Resuscitation (ILCOR) recommends the use of TH for comatose survivors after OHCA due to shockable rhythms (VF/VT). Furthermore, ILCOR stated that TH might also be beneficial for non-shockable rhythms or in-hospital cardiac arrest (IHCA) [3]. In 2008, the intensive care unit (ICU) at Holbaek Hospital, like most ICU in Denmark, implemented these recommendations. Hence, all comatose patients who were resuscitated after cardiac arrest were treated with TH, regardless of whether the patient fulfilled the criteria of the original randomised trials (shockable rhythms and OHCA) or not (non-shockable rhythms or IHCA). However, evidence on whether TH can improve the prognosis in patients with non-shockable rhythms or IHCA is sparse [4]. The aim of the present study was to assess the prevalence and prognosis of patients with non-shockable rhythms or IHCA after implementation of TH in a real life setting.

METHODS

Patients

During a five-year period from November 2008 to November 2013, we included 72 consecutive patients, admitted to the ICU at Holbaek Hospital after cardiac arrest and successful resuscitation. Return of spontaneous circulation (ROSC) with a systolic blood pressure exceeding 90 mmHg for five minutes was defined as successful resuscitation. Furthermore, the cardiac arrest had to be witnessed, the estimated interval from the patient's collapse to the first attempt at resuscitation had to be less than 15 minutes and ROSC should be within 60 minutes. All patients were unconscious (a score of < 9 on the Glasgow Coma Scale) upon admission to the ICU. Patients were included regardless of the initial cardiac rhythms (both shockable rhythms and non-shockable rhythms were included) and location of the cardiac arrest (both patients with OHCA and IHCA were included). Patients who had an immediate need for primary percutaneous coronary intervention (pPCI) were transferred to Rigshospitalet or Gentofte Hospital (tertiary referral centres), and were not included. Furthermore, patients with terminal illness, severe haematological disease, intracranial bleeding, severe bleeding or severe septic shock were excluded.

Treatment

Cooling was initiated immediately if patients fulfilled the above-mentioned criteria. The target temperature (32-34 °C measured in the bladder) was achieved by packing

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ice around the head, neck, torso and limbs; by intravenous infusion of crystalloids with a temperature of 4 °C; and by cooling patches. If possible, the target temperature was maintained for 24 hours followed by gradual rewarming by 0.5 °C per hour until normothermia (37 °C). Standard sedation and neuromuscular blockade were used in order to prevent shivering and to reduce oxygen consumption. Furthermore, all patients received standard treatment with antibiotics (cefuroxime and metronidazole), antithrombotics (low molecular weight heparin) and proton pump inhibitors as prophylaxis.

Outcome

In order to assess the prevalence and prognosis in patients with non-shockable rhythms or IHCA, the patients were stratified into two groups; patients who fulfilled the criteria of the original randomised trials (shockable rhythms and OHCA) [1, 2] and patients who did not fulfil the criteria (non-shockable rhythms or IHCA). The primary outcome was survival within six months and neurologic outcome. Data were collected using nationwide registers and medical journals. Neurologic outcome within six months was defined by the Pittsburgh Cerebral Performance Category (CPC): 1 (good recovery), 2 (moderate disability), 3 (severe disability), 4 (a vegetative state), and 5 (death) [5]. Favourable neurologic outcome was defined as CPC 1 or 2.

Statistical analysis

Comparison between groups was performed by Student's t-test and chi-square test. All continuous variables were expressed as mean values ± standard deviation and categorical variables as frequencies (percentages). Kaplan-Meier survival curves were compared between groups with the use of log-rank test, and Cox analyses were performed as appropriate. A p-value ≤ 0.05 was considered statistically significant. All analyses were performed using SPSS software (SPSS system for Mac, release 20.0.0, SPSS Inc. Headquarters, Chicago, Illinois).

Ethics

The study was approved by the Danish Data Protection Agency, record number 3-3013-521/1.

Trial registration: not relevant.

RESULTS

During a five-year period, 72 patients were included. Almost two thirds (63%) of the included patients had non-shockable rhythms or IHCA and did not fulfil the guideline criteria of the original randomised studies. After initial cooling, six of the 26 patients with shockable rhythms and OHCA were transferred to a tertiary referral centre for coronary revascularisation, whereas none of the patients with non-shockable rhythms or IHCA were in need of coronary revascularisation.

The patients' baseline characteristics are presented in **Table 1**. Patients with non-shockable rhythms or IHCA had a higher prevalence of lung and kidney disease before hospitalisation, and the prevalence of in-hospital acquired infection and acute kidney injury was also higher compared to patient with shockable rhythms and OHCA. Patients with shockable rhythms and OHCA, on the other hand, had a higher prevalence of acute coronary syndrome, in-hospital heart failure, history of ischaemic heart disease, history of arrhythmia and history of heart failure. Thus, patients with shockable rhythms and OHCA were characterised by a high prevalence of heart disease and cardiac events, whereas patients with non-shockable rhythms or IHCA were characterised by a high prevalence of non-cardiac disease.

Eleven of the 26 patients with shockable rhythms

TABLE 1

Baseline characteristics with comparison of patients with shockable rhythms and OHCA and patients with non-shockable rhythms or IHCA.

	Shockable rhythms and OHCA	Non-shockable rhythms or IHCA	p-value
Total, n	**26**	**46**	
Baseline characteristics			
Age, yrs, mean ± SD	64 ± 14	67 ± 14	NS
Male, n (%)	23 (88)	15 (33)	< 0.001
Hypertension, n (%)	18 (69)	26 (57)	NS
Diabetes, n (%)	6 (23)	13 (28)	NS
Ischaemic heart disease, n (%)	15 (58)	15 (33)	NS
Arrhythmia, n (%)	4 (15)	4 (8.7)	NS
History of heart failure, n (%)	8 (31)	8 (17)	NS
History of CNS disease, n (%)	5 (19)	8 (17)	NS
History of lung disease, n (%)	5 (19)	25 (54)	0.006
History of kidney disease, n (%)	1 (3.8)	7 (15)	NS
In-hospital characteristics			
ROSC within 15 min., n (%)	10 (38)	18 (39)	NS
Length of stay in hospital, days, mean ± SD	12 ± 13	10 ± 12	NS
Length of stay in ICU, days, mean ± SD	4.6 ± 3.7	5.9 ± 5.0	NS
Acute coronary syndrome, n ()	15 (57)	10 (22)	0.004
Heart failure in-hospital, n (%)	14 (54)	6 (13)	< 0.001
ARDS in-hospital, n (%)	0 (0)	3 (6.5)	NS
SIRS, n (%)	13 (50)	26 (57)	NS
Infection in-hospital, n (%)	1 (3.8)	13 (28)	0.013
Acute kidney injury, n (%)	3 (12)	16 (35)	0.05
Seizures, n (%)	9 (35)	11 (24)	NS
OHCA, n (%)	26 (100)	21 (45)	< 0.001
Outcome at 6 months			
Survival, n (%)	11 (42)	5 (11)	0.003
Favourable neurologic outcome, n (%)	11 (42)	4 (8.7)	0.001

ARDS = adult respiratory distress syndrome; CNS = central nervous system; ICU = intensive care unit; IHCA = in-hospital cardiac arrest; NS = not significant; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; SD = standard deviation; SIRS = systemic inflammatory response syndrome.

and OHCA (42%) survived with a favourable outcome, versus only four out of 46 (8.7%) in patients with non-shockable rhythms or IHCA. This significant difference between the two groups is illustrated in the Kaplan-Meier plot in **Figure 1**. Unsurprisingly, the mortality rate (hazard ratio) in patients with non-shockable rhythms or IHCA was significantly higher than in patients with shockable rhythms and OHCA (hazard ratio 2.34 (1.29-4.27), p = 0.005).

Almost a third (29%) of the included patients had an OHCA with an initial non-shockable rhythm. Despite successful resuscitation and subsequent treatment with HT, none (0%) of these patients survived with a favourable neurologic outcome (**Figure 2**).

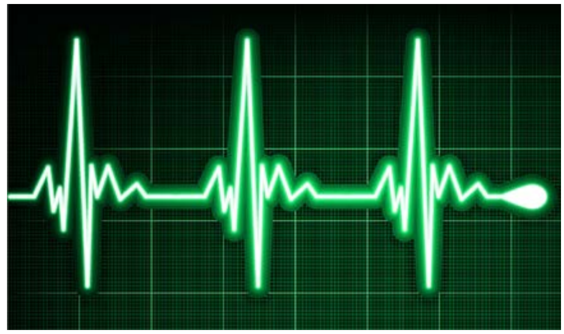
DISCUSSION

TH has been the cornerstone in the treatment of unconscious survivors after cardiac arrest since the publication of two landmark studies in 2002 which concluded that induced hypothermia (32-34 °C) improves survival and neurologic outcome in patients with shockable rhythms and OHCA [1, 2]. These trials substantiate the possible neuroprotective effect of cooling described in animal studies [6] and among newborns [7]. Subsequently, international guidelines (ILCOR) recommended the use of TH in all unconscious survivors after cardiac arrest, including patients with non-shockable rhythms or IHCA. However, despite substantial research, the optimal temperature and target population remains to be defined.

The presented study is the largest observational study conducted in Denmark after implementation of TH. It reflects the impact TH has in a clinical setting when applied to an entire cardiac arrest population in a hospital without access to invasive cardiology. Almost two thirds (63%) of the included patients had non-shockable rhythms or IHCA and did not fulfill the criteria of the original randomised studies upon which the current guidelines are based. Furthermore, only 8.7% of these patients survived with a favourable neurologic outcome. Nearly one third (29%) of the included patients had an OHCA with an initial non-shockable rhythm. Despite successful resuscitation and subsequent treatment with TH, none (0%) of these patients survived with a favourable neurologic outcome. These findings suggest that not all patients may benefit from cooling after cardiac arrest.

After initial cooling, almost a fourth (23%) of the patients with shockable rhythms and OHCA were transferred to a tertiary referral centre for coronary revascularisation indicating that perhaps post-cardiac arrest treatment of these patients should in general be carried out at tertiary centres with access to invasive cardiology. This was also the conclusion in a large Danish register study [8].

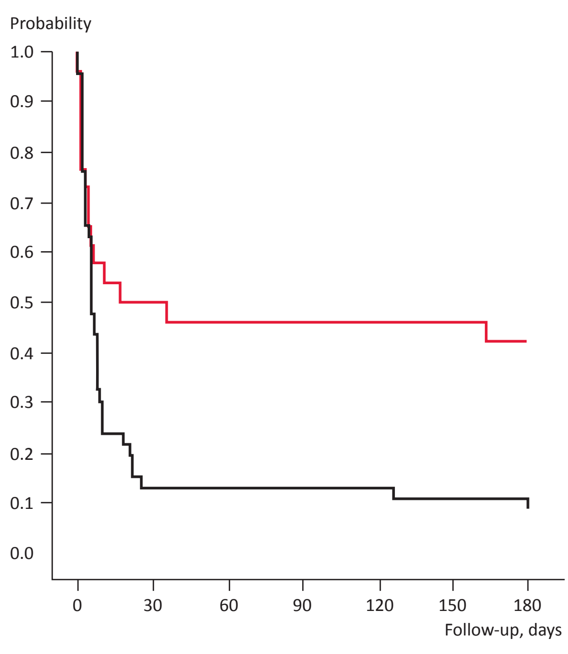
Patients resuscitated after cardiac arrest with non-shockable rhythms or IHCA have a consistently higher mortality than patients with shockable rhythms and OHCA [8-10]. OHCA due to shockable rhythms is usually the result of cardiac causes such as arrhythmia or acute myocardial ischaemia. In contrast, patients with non-shockable rhythms or IHCA represent a more heterogeneous population with a wider variety of causes, such as hypoxia (respiratory failure), infection/sepsis, hypovolaemia, pulmonary embolism or cardiac tamponade. These causes are often associated with major co-mor-



Therapeutic hypothermia after cardiac arrest in a real-life setting.

FIGURE 1

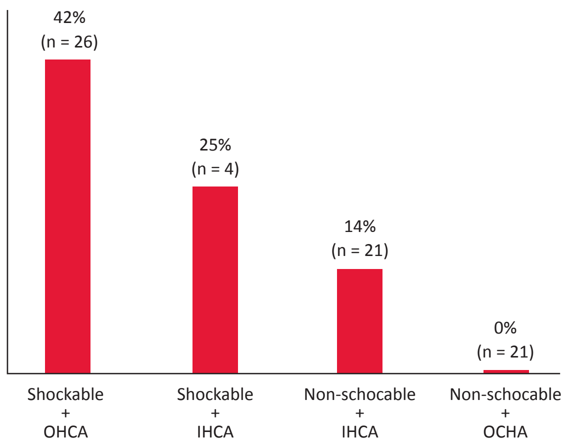
Kaplan-Meier plot showing the cumulative probability of survival with a favourable neurologic outcome (cerebral-performance category 1 or 2) for patients with shockable rhythms and out-of-hospital cardiac arrest, and patients with non-shockable rhythms or in-hospital cardiac arrest; p < 0.001 (log-rank).



IHCA = in-hospital cardiac arrest; OHCA = out-of-hospital cardiac arrest.

FIGURE 2

Patients are stratified according to the initial cardiac rhythm (shockable/non-shockable) and the location of the cardiac arrest (OHCA/IHCA). The percentage of patients surviving with a favourable neurologic outcome is presented for each of the four groups (n, total number of patients in each group).



IHCA = in-hospital cardiac arrest; OHCA = out-of-hospital cardiac arrest.

bidities, which could reduce the chance of survival after cardiac arrest, regardless of successful resuscitation and treatment with TH. Moreover, TH is associated with several complications such as impairment of the coagulation and immune system, hyperglycaemia, electrolyte abnormalities, arrhythmias and seizures [11-14] , and patients with non-shockable rhythms or IHCA may be more vulnerable to such complications due to a higher prevalence of co-morbidity. Finally, non-shockable rhythms (asystole and pulseless electrical activity) are sometimes the result of deterioration of shockable rhythms (VF/VT) and may therefore indicate a long collapse-to-resuscitation time due to insufficient resuscitation, which is also associated with a poor outcome. Similar difference between groups was also found in the present study where patients with shockable rhythms and OHCA were characterised by a high prevalence of heart disease and cardiac events, whereas patients with non-shockable rhythms or IHCA were characterised by a high prevalence of non-cardiac disease. Hence, not surprisingly, we found that the probability of survival with a favourable neurologic outcome after cardiac arrest is significantly reduced in patients with non-shockable rhythms or IHCA compared to patients with shockable rhythms and OHCA, when all patients were treated with TH. To summarise, patients with non-shockable rhythms or IHCA may simply be too ill to benefit from cooling, and for some patients it may even be harmful.

The evidence on whether patients with non-shockable rhythms or IHCA benefit from cooling is sparse. No randomised studies specifically designed to assess the benefit of TH in this population have been conducted. However, series of observational studies have addressed the subject. The results from these studies are conflicting, varying from a small benefit in some studies [13, 15, 16] to no benefit or even a harmful effect in other studies [17, 18]. However, a sub-study of the Target Temperature Management (TTM) trial showed a poor prognosis and no effect of target temperature management at 33 °C compared to 36 °C in patients with non-shockable rhythms and OHCA [19], indicating that TH may not benefit patients with initial non-shockable rhythms. In general, this lack of evidence may result in unnecessary or even harmful treatment.

Our scepticism towards the current guidelines is in line with the newly published TTM trial [20]. In this well-designed RCT (the largest one to date), 939 patients with OHCA of presumed cardiac cause who remained comatose after resuscitation were randomised to targeted temperature management at either 33 °C or 36 °C. No difference in mortality or neurological outcome could be demonstrated between patients targeting a temperature of 33 °C and patients targeting a temperature of 36 °C. These results have challenged the original randomised studies upon which the current guidelines are based. One of the main points of criticism in the original studies was a lack of temperature management in controls, meaning that some of the effect seen in these studies may be a result of untreated fever in controls. The TTM study supports this important point indicating that patients with fever after cardiac arrest may benefit the most from TH. Therefore, one could hypothesise that patients with fever and OHCA with a presumed cardiac cause may benefit the most from TH after cardiac arrest. However, further studies, particularly in patients with cardiac arrest of non-cardiac cause (non-shockable rhythms or IHCA), are necessary in order to define which patients benefit from TH after cardiac arrest.

Limitations

The present observational cohort study has several limitations. First, all patients received treatment with hypothermia; hence there was a lack of controls and even though the prognosis among patients with non-shockable rhythms or IHCA seems poor one cannot rule out a small effect of cooling. Data were collected by lookup in national registers and medical journals where the accuracy of data depends on correct registration and interpretation of guidelines done by clinical physicians. In addition, patients in need of pPCI were transferred immediately to tertiary referral centres for treatment, resulting in selection bias. This may explain why the prevalence of patients with shockable rhythms and OHCA was relatively low in the present study.

CONCLUSIONS

In a real life setting, the majority of resuscitated patients receiving TH do not fulfill the criteria of the original studies upon which the current guidelines are based. These patients have a poor outcome, indicating that not all patients may benefit from cooling. This may result in un-ethical or even harmful treatment among subgroups of patients treated with TH after cardiac arrest.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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