

REVIEW

Therapeutic hypothermia: is it effective for non-VF/VT cardiac arrest?

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Introduction

Sudden cardiac death represents a major health problem. In adults, the prevalence of out-of-hospital cardiac arrest (OHCA) attended by the emergency medical services (EMS) ranges from 52 to 112 per 100,000 person-years in developed countries [1], whereas the prevalence of adult in-hospital cardiac arrest (IHCA) ranges from 1 to 5 per 1,000 patient admissions [2].

Mortality from cardiac arrest exceeds 90 % in OHCA [1, 3] and 70 % in most studies on IHCA [4–6]. Patients who have a shockable rhythm, i. e., ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), on initial electrocardiogram (EKG) have a consistently higher survival than those whose initial cardiac rhythm is non-shockable, i. e., asystole or pulseless electrical activity (PEA).

More than two-thirds of initially resuscitated patients die before hospital discharge [7,8]. The major causes of hospital mortality are post-resuscitation brain and myocardial dysfunction [9,10]. Mild therapeutic hypothermia can reduce the severity of post-resuscitation brain injury and improve survival in patients who remain comatose after resuscitation from cardiac arrest. In 2002, two randomized clinical trials showed improved neurological outcome [11,12] in a total of 350 comatose adults resuscitated from OHCA who were cooled to 32–34 °C for 12–24 hours shortly after recovery of spontaneous circulation. The largest of these trials [12] also showed a significant reduction in mortality within six months in patients treated with mild therapeutic hypothermia. Both these trials included only patients who had VF/VT as the initial rhythm.

Based on these results, subsequently confirmed by a meta-analysis [13], the International Liaison Committee

on Resuscitation (ILCOR) recommended in 2003 the use of mild therapeutic hypothermia for all comatose survivors after OHCA due to VF/VT [14]; this recommendation was confirmed in the current 2010 Guidelines for Cardiopulmonary Resuscitation [15]. However, only 25–30 % of OHCA patients have VF/VT as the initial recorded cardiac rhythm [1], and this percentage has decreased in recent years [16,17], partly because of the advent of implantable cardioverter-defibrillators for the prevention and treatment of patients at risk of lethal arrhythmias [18]. The prevalence of VF/VT rhythms in IHCA does not exceed 25–30 % either [2]. For the remaining 70–75 % of patients who undergo cardiac arrest with non-VF/VT rhythms, indications for receiving therapeutic hypothermia after resuscitation are less clear.

Hypothermia for non-VF/VT cardiac arrest

The evidence on whether use of mild therapeutic hypothermia could improve prognosis in comatose patients resuscitated from non-VF/VT cardiac arrest is sparse. We identified 15 observational studies (Table 1) and 2 randomized trials.

Randomized clinical trials

Use of mild therapeutic hypothermia for the treatment of patients resuscitated from non-VF/VT cardiac arrest has been described in two randomized trials, even though neither was specifically designed to assess the benefit of mild therapeutic hypothermia in this patient population. One trial was a feasibility study on a helmet device for inducing hypothermia after resuscitation [19], the other examined the effect of isovolemic high-volume hemofiltration alone or combined with mild therapeutic hypothermia to improve survival after cardiac arrest [20]. These trials included a total of only 44 patients with non-VF/VT rhythms. Within this small subgroup, patients treated with mild therapeutic hypothermia had a higher survival rate at six months than did controls (5/22

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Table 1. Characteristics of 15 observational studies including data on use of mild therapeutic hypothermia in patients with non-ventricular fibrillation/ventricular tachycardia (VF/VT) cardiac arrest

Author [Reference]	Arrest location	Patients	Non-VF/VT		Initiation of hypothermia	Cooling method	Control group	Definition of poor outcome	Length of follow-up
			Total	Cooled					
Holzer 2006 [27]	Mixed (OHCA 67%)	1,038	534	28	In-hospital	Internal	Concurrent	CPC 3–5	30 days
Oddo 2006 [21]	OHCA	109	23	12	In-hospital	External	Historical	CPC 3–5	Discharge
Heer 2007 [26]	Mixed	76	18	10	In-hospital	Internal	Historical	NA	Discharge
Sunde 2007 [29]	OHCA	119	15	6	In-hospital	Mixed	Historical	CPC 3–5	Discharge
Arrich 2007 [23]	Mixed (OHCA 83%)	587	197	124	In-hospital	Mixed	Concurrent	CPC 3–5	Discharge
Rittenberger 2008 [38]	Mixed (OHCA 56%)	241	81	42	In-hospital	Mixed	Concurrent	Discharged to a nursing home	Discharge
Storm 2008 [28]	OHCA	126	49	18	In-hospital	Mixed	Historical	CPC 3–5	Discharge
Don 2009 [24]	OHCA	491	313	122	In-hospital	External	Historical	CPC 2–5	Discharge
Whitfield 2009 [30]	OHCA	123	28	15	Pre/In-hospital	Mixed	Historical	Discharged to a nursing home	Discharge
Gaieski 2009 [39]	OHCA	38	18	9	In-hospital	Mixed	Historical	CPC 3–5	Discharge
Bro-Jepesen 2009 [25]	OHCA	156	48	27	Pre/In-hospital	Mixed	Historical	CPC 3–5	6 months
Derwall 2009 [37]	OHCA	68	28	13	In-hospital	Mixed	Concurrent	CPC 3–5	14 days
Dumas 2011 [33]	OHCA	1,145	437	261	In-hospital	External	Historical	CPC 3–5	Discharge
Storm 2012 [34]	Mixed (OHCA 73%)	387	175	87	In-hospital	Mixed	Historical	CPC 1–2	90 days
Lundbye 2012 [35]	Mixed (OHCA 52%)	100	100	52	In-hospital	Internal	Historical	CPC 3–5	Discharge

OHCA: out-of-hospital cardiac arrest; CPC: Cerebral Performance Category.

vs. 2/22; risk ratio [RR] for mortality 0.85 [0.65–1.11] $p = 0.24$).

Observational studies

A series of observational studies evaluated the effects of mild therapeutic hypothermia in non-VF/VT patients (Table 1). In a retrospective analysis from Oddo et al. [21] of a database on the implementation of mild therapeutic hypothermia in an intensive care unit (ICU), the rates of good neurological outcome (Cerebral Performance Category [CPC] 1–2 [22]) in a small subgroup of patients resuscitated from non-VF/VT arrest and treated with mild therapeutic hypothermia was not significantly better than that of historical controls (2/12 vs. 1/11; $p = 0.99$).

In 2007, the results of the European Resuscitation Council Hypothermia After Cardiac Arrest Registry (HACA-R) were published [23]. This multicenter observational study included data from 19 participating centers on 587 patients resuscitated from cardiac arrest, around 18% of which had occurred in hospital. The non-VF/VT subgroup included 197 subjects, 124 (63%) of whom were treated using mild therapeutic hypothermia. The rate of survival to hospital discharge was significantly higher in mild therapeutic hypothermia-treated patients

(45/124 (35%) vs. 14/73 (19%); $p = 0.023$). The rate of the combined endpoint of death (CPC = 5) and poor neurological outcome (CPC 3–4) was also lower – although not significantly – in the mild therapeutic hypothermia group (89/124 [71%] vs. 59/73 [81%] $p = 0.21$). In this study, only univariate analysis was performed, so no correction was made for pre- and intra-arrest potential confounders. Another limitation was the risk of selection bias, because the choice of using hypothermia in a given patient was left to the discretion of the treating physician.

In 2009, a large, retrospective study by Don et al. [24] on implementation of mild therapeutic hypothermia in a community hospital during a five year-period was published. The study included a total of 491 patients with OHCA with all rhythms, of whom 313 (74%) had non-VF/VT cardiac arrest. Patients enrolled after implementation of the therapeutic hypothermia protocol were compared with historical controls. Results showed that whereas in patients with VF/VT the hypothermia period was associated with significantly higher rates of survival to hospital discharge and favorable neurological outcome as compared to the pre-hypothermia period (44/81 [54.3%] vs. 36/93 [38.7%]; $p = 0.04$ and 28/81 [34.6%] vs. 14/93 [15%]; $p = 0.01$, respectively), there were no

significant improvements in patients resuscitated from non-VF/VT rhythms (26/122 [21 %] vs. 37/191 [19 %], $p = 0.78$ and 14/122 [11 %] vs. 17/191 [9 %], $p = 0.82$, respectively). Moreover, results of multivariable analysis showed a slight trend towards a worse outcome for the mild therapeutic hypothermia period in patients with non-VF/VT rhythms (favorable neurological outcome odds ratio [OR] 0.82 [0.41–1.60]; survival to discharge OR 0.92 [0.37–2.32]).

Other smaller observational studies on mild therapeutic hypothermia were carried out between 2006 and 2009 [25–30]. None of these studies was designed to specifically investigate the association between mild therapeutic hypothermia and prognosis of non-VF/VT rhythms. The majority of these studies documented a non-significant trend towards better outcome when mild therapeutic hypothermia was used in patients with non-VF/VT cardiac arrest.

A recent systematic review and meta-analysis by Kim et al. [31] evaluated the two randomized studies reported above and 12 non-randomized studies for a total of 1,336 non-VF/VT patients, 412 (30.8 %) of whom were treated using mild therapeutic hypothermia. The quality of evidence was assessed using the GRADE methodology [32]. The results showed that the quality of evidence in all studies was very low. Most of the studies had substantial risks of bias and 9/12 had a high degree of imprecision, because of their small sample size. Pooled data from the two small randomized studies showed a non-significant trend toward a lower 6-month mortality with mild therapeutic hypothermia (RR 0.85 [0.65–1.11]). Meta-analysis of the 12 observational studies showed a significant reduction in hospital mortality (RR 0.84 [0.78–0.92]) and a non-significant trend towards better neurological outcome (RR for poor neurological outcome 0.95 [0.90–1.01]) after mild therapeutic hypothermia. The authors concluded that mild therapeutic hypothermia was associated with reduced in-hospital mortality for adult patients resuscitated from non-shockable cardiac arrest, but also suggested caution in interpreting the results, given a substantial risks of bias and the low quality of the evidence.

Results of the most recent studies

Three very recent studies that were not included in the systematic review by Kim et al. [31] reported conflicting results on the potential benefit of mild therapeutic hypothermia in patients with non-VF/VT cardiac arrest. A first study by Dumas et al. [33] reported data from a prospective French database including 1,145 OHCA patients, 437 of whom were non-VF/VT patients. The association between mild therapeutic hypothermia and good neurological outcome at discharge (CPC 1 or 2) was quantified by logistic regression analysis. Mild therapeutic

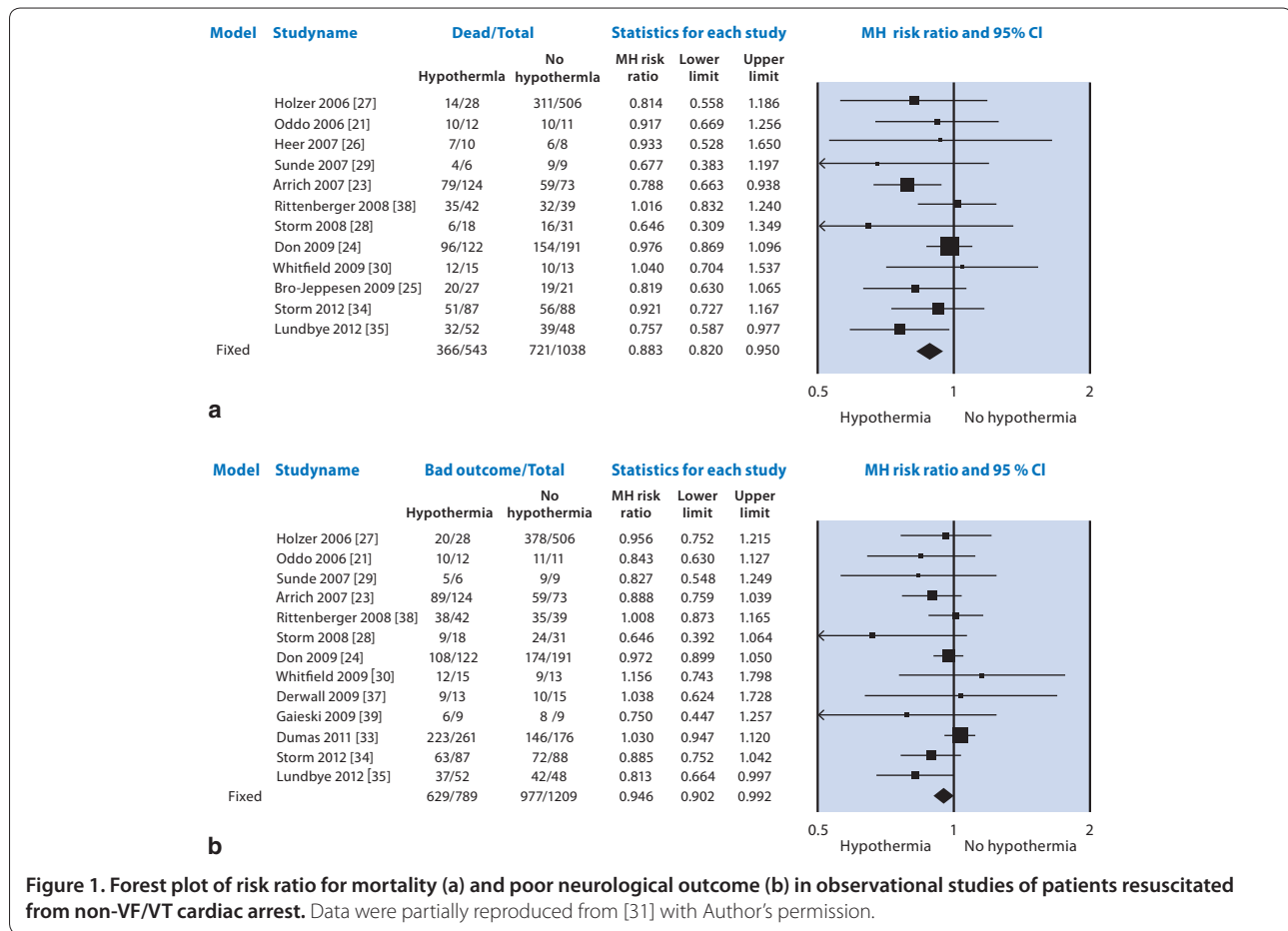
hypothermia was induced in 457/708 (65 %) patients with VF/VT and in 261/437 (60 %) with non-VF/VT. After adjustment for confounders, the results showed that whereas mild therapeutic hypothermia was associated with a significantly better neurological outcome at discharge in VF/VT patients, there was a trend towards a worse outcome in non-VF/VT patients (OR 1.90 [1.18–3.06] vs. 0.71 [0.37–1.36]).

Another prospective single-center observational study was conducted by Storm et al. [34] in a university hospital setting with historical controls. The paper enrolled 387 consecutive patients with all rhythms who had been admitted to the ICU after cardiac arrest. Mild therapeutic hypothermia was induced in 201 patients (87 with non-VF/VT), who were compared with 186 historical controls (88 with non-VF/VT). Univariate analysis showed a non-significant trend towards better neurological outcome in non-VF/VT patients treated with mild therapeutic hypothermia (24/87 [27.8 %] vs 16/88 [18 %], $p = 0.17$). On Cox regression analysis, however, the risk for poor neurological outcome at discharge in the two groups was almost identical (hazard ratio [HR] 0.98 [0.53–1.50]). Kaplan-Meier analysis revealed no differences in 90-day survival with or without mild therapeutic hypothermia ($p = 0.82$).

Finally, a recent small single-center observational study by Lundbye et al. [35] compared neurological outcome and survival at hospital discharge in 52 non-VF/VT cardiac arrest patients treated using mild therapeutic hypothermia compared with 48 historical controls who did not receive mild therapeutic hypothermia. In contrast with the previous two studies, the rates of good neurological outcome (15/52 [29 %] vs. 6/48 [13 %]; $p = 0.021$) and survival to discharge (20/52 [38 %] vs. 9/48 [19 %]; $p = 0.03$) were significantly higher in patients treated with mild therapeutic hypothermia. These results were confirmed after controlling for confounders using binomial logistic regression (OR 4.35 [1.10–17.24], $p = 0.04$ and OR 5.65 [1.66–19.23], $p = 0.006$, respectively).

The Forest plots in Fig. 1a, b summarize the results of 12 observational studies reporting survival to discharge (1,581 patients, Fig. 1a) and of 13 observational studies reporting neurological outcome (1,998 patients, Fig. 1b). Data pooled according to a fixed effect model show a significant reduction in the RR for hospital mortality (0.88 [0.82–0.95]) and a smaller but significant reduction in RR for poor neurological outcome (0.95 [0.90–0.99]) in patients treated using mild therapeutic hypothermia. However, in spite of pooled results favoring treatment, the effect is not consistent, with large studies showing increased RR for poor neurological outcome associated with use of mild therapeutic hypothermia [33] (Fig. 1b).

In comparison with the results of randomized trials in VF/VT patients [36], analysis of the available evidence shows that use of mild therapeutic hypothermia in



comatose patients resuscitated from non-VF/VT cardiac arrest is associated with a small effect size, particularly as regards neurological outcome, with several studies [24,30,33,37,38] suggesting no effect or even a possible harm from mild therapeutic hypothermia. There are many possible explanations for this observation. One explanation could be that patients who undergo a cardiac arrest with non-VF/VT rhythms represent a more heterogeneous population as compared to those with a VF/VT arrest. Sudden death due to VF/VT is usually the result of cardiac causes, such as arrhythmia or acute myocardial ischemia, whereas non-VF/VT rhythms (asystole or PEA) have a wider variety of causes, such as hypoxia, hypovolemia, sepsis, pulmonary thromboembolism, or cardiac tamponade. These causes are often associated with major comorbidities, which could reduce the chances of patient survival after resuscitation, regardless of the protective effect of mild therapeutic hypothermia. Moreover, cardiac arrest from these causes is often preceded by generalized hypoxia or hypoperfusion, which may further worsen cerebral anoxic damage. Finally, since asystole represents the final evolution of all cardiac arrest rhythms, its presence may indicate a long

collapse-to-resuscitation interval and/or poor or absent bystander resuscitation, both of which are associated with a high risk of irreversible neurological damage. In some studies, therefore, non-VF/VT patients could have been simply too ill to benefit from mild therapeutic hypothermia.

Heterogeneity observed in study results may also be explained by differences in case mix and in cooling protocols. For example, some studies included only OHCA patients, whereas others included both IHCA and OHCA (see Table 1). Two of the studies that documented lack of benefit from mild therapeutic hypothermia used the external surface cooling method, which may require longer times to achieve the target temperature than with intravascular cooling.

Finally, apart from two trials with minimal sample sizes, all the published studies on mild therapeutic hypothermia for non-VF/VT arrest are observational. This makes controlling of confounders extremely difficult to achieve and introduces further sources of bias. Studies in which the control group was represented by concurrent patients not treated using mild therapeutic hypothermia are prone to selection bias, and in those with historical

controls, the results may reflect secular trends in patient or disease characteristics or changes in resuscitation practice rather than the effect of the study intervention.

To be correctly addressed, the question as to whether mild therapeutic hypothermia may be beneficial in patients with asystole or PEA as the initial cardiac rhythm will require a purposely designed, high-quality randomized controlled trial. However, in order to demonstrate an increase in survival from 25 % to 30 % with a 0.05 risk of a type-1 error (alpha) and a 0.20 risk of type-II error (beta) using univariate analysis, a minimum of 1,100 patients resuscitated from non-VF/VT would be required. Such a large sample size would be difficult to collect, considering that only about 10 % of patients resuscitated from cardiac arrest of all rhythms survive to hospital admission [8]. Moreover, this trial may even raise ethical issues, since pooled results from observational studies suggest a modest but significant benefit from mild therapeutic hypothermia in non-FV/VT cardiac arrests.

Conclusions

Non-VF/VT are the most common initial cardiac rhythms recorded in both in-hospital and out-of-hospital cardiac arrests. Unfortunately, patients with non-VF/VT rhythms also represent the majority of those who die despite resuscitation, and interventions able to improve the prognosis of this patient category are eagerly awaited. Whereas mild therapeutic hypothermia has been consistently demonstrated to improve outcomes after VF/VT cardiac arrest, its use in patients with non-VF/VT arrest has produced conflicting results. Pooled data from available studies show that the use of mild therapeutic hypothermia for 24 hours in comatose patients resuscitated from non-VF/VT arrest was associated with a 15 % reduction in hospital mortality and with a minimal, albeit significant improvement in neurological outcome at discharge. The quality of evidence supporting these results, however, is very poor, since it is based almost exclusively on observational studies, most of which were not specifically designed to evaluate the benefit of mild therapeutic hypothermia in non-VF/VT patients. Randomized controlled trials of adequate sample size are necessary to address this question.

Competing interests

The authors declare that they have no competing interests.

List of abbreviations used

CPC: cerebral performance category; EKG: electrocardiogram; EMS: emergency medical services; HACA-R: Hypothermia After Cardiac Arrest Registry; HR: hazard ratio; ICU: intensive care unit; IHCA: in-hospital cardiac arrest; ILCOR: International Liaison Committee on Resuscitation; OHCA: out-of-hospital cardiac arrest; PEA: pulseless electrical activity; RR: risk ratio; VF: ventricular fibrillation; VT: ventricular tachycardia.

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