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EDITORIAL

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To cool or not to cool non-shockable cardiac arrest patients: it is time for randomized controlled trials

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Based on remarkable effects mostly observed in shockable patients, therapeutic hypothermia (TH) has been widely proposed for comatose patients after cardiac arrest (CA) [1]. Although used in patients who have been resuscitated from a non-shockable out-of-hospital CA (OHCA), there are no large randomized controlled trials (RCTs) evaluating the clinical impact of TH in this situation. As a result, the use of TH in OHCA patients with a non-shockable rhythm is still controversial, as reflected by the discrepancy between practice, recommendations and expert opinion [1, 2].

In this issue of the journal, Vaahersalo et al. [3] report a large multicentre observational study, covering 98 % of the Finnish adult population, in which they prospectively evaluated over a 1-year period the post-resuscitation cares, the use of TH and the outcomes in all OHCA patients treated in the participating ICUs in Finland. Interestingly, in their population of 548 adult OHCA patients treated in an ICU, the proportion of shockable patients was higher than the proportion of non-shockable patients, in spite of pre-hospital shockable rhythms now representing the minority of OHCA patients. Additionally, TH was performed in 85.8 % of shockable patients and 31.4 % of non-shockable patients. Similar to previous findings in pivotal studies, TH was associated with a better prognosis in the shockable group. However, the authors could not find any significant beneficial effects of TH in non-shockable patients: 80.6 % of patients with TH experienced an unfavourable outcome (i.e. cerebral performance categories: CPC in the range 3–5) versus 84.0 % without TH ($p = 0.56$). This result was unchanged after adjustment with a propensity analysis and in patients with CPC 1. Although the study was not initially planned nor powered to detect an effect, the authors conclude that these results do not support the use of TH in non-shockable patients (the maximal potential benefit was a risk reduction of less than 15 % in this population in which 17 % of the patients experienced a 1-year favourable outcome).

Can these interesting results solve the debate on the use of TH in non-shockable patients? Serious limitations persist, although some are discussed by the authors. In the propensity analysis, several strong predictors of outcome, including witnessed arrest, bystander cardiopulmonary resuscitation and "time to return of spontaneous circulation" (ROSC), were no longer significant as well as the use of TH. More importantly, detailed data regarding achievement of goal temperature in the groups were not reported and the decision to use TH in the non-shockable group was left to the discretion of the bedside physician in spite of being of major importance in this heterogeneous group. Indeed, a non-shockable rhythm may be the first documented rhythm following a severe CA of non-cardiac aetiology or following a prolonged ischaemia period (prolonged time to ROSC) occurring after a shockable

Table 1 Pros and cons of TH in patients with non-shockable OHCA

Reason	TH strategy (target 32–34 °C)	Normothermia strategy
Pathophysiological arguments: protective effects in asphyxic animal CA models (in terms of histological and neurobehavioural scores, and survival)	+	−
Beneficial effects on survival and neurological function obtained in neonatal hypoxic-ischaemic encephalopathy (mimicking asphyxia)	+	−
Available RCTs[a]	?	?
Available meta-analyses[a]	? (results disputable or insufficiently powered)	−
Available non-randomized studies (registries, observational, matched studies…)[a]	+ (most positive or nonsignificant studies are small)	? (nonsignificant negative findings in some small studies)
Impact of different targeted temperature management (35–36 °C…)[a]	?	?
No other available treatment to date[a]	+	?
Possible TH-related side effects (risk/benefit ratio)	−	+
Possible TH-related increase in time to recovery of consciousness	−	+
Possible TH-related increase in duration of hospitalization	−	+
Possible TH-related increase in ICU cost	?	+
Could prevent neurological damage (increase in likelihood of favourable outcome, CPC 1-2)[a]	+	−
Could save life (decrease in likelihood of unfavourable outcome, CPC 5)[a]	+	?
Severity of the underlying disease (poor prognosis altering the possible impact of the treatment)[a]	+ (more TH treatment justified)	? (TH not useful or futile)
Ethical considerations (futility/benefit ratio)[a]	?	?

TH, therapeutic hypothermia; OHCA, out-of-hospital cardiac arrest; RCTs, randomised controlled trials; ICU, intensive care unit; CPC, cerebral performance category; NS, not significant; +, arguments in favour of the strategy; −, arguments against the strategy; ?, insufficient data to conclude

[a] In patients with non-shockable CA

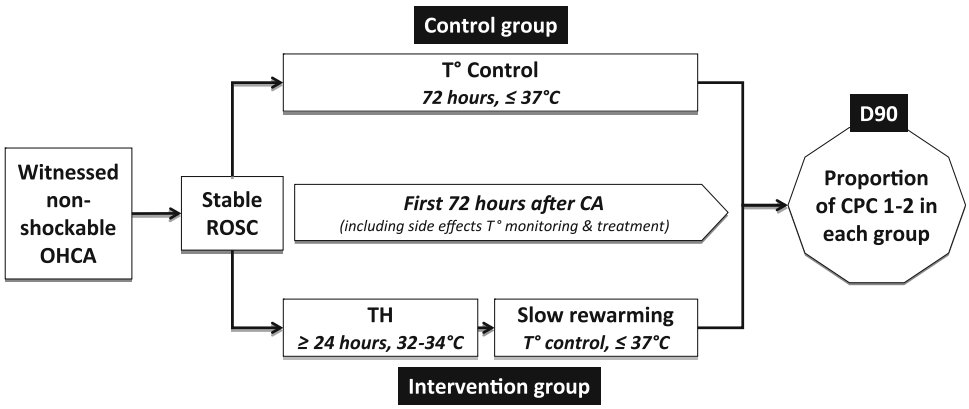

Fig. 1 Multicentre randomized controlled trial proposal for TH evaluation in patients with non-shockable OHCA. According to the meta-analysis by Kim et al. [8], more than 1,250 unselected patients with non-shockable CA per group would be needed to obtain a 5 % difference between groups (good outcome in 25–30 % in favour of the TH group) with an 80 % power and 5 % alpha risk. CA, cardiac arrest; OHCA, out-of-hospital cardiac arrest; TH, therapeutic hypothermia; CPC, cerebral performance category; ROSC, return of spontaneous circulation

initial CA. These situations can lead to multiple organ failure or severe brain damages. Testori et al. [4] have recently reported in witnessed OHCA patients a greater benefit of TH if the "no flow" period was prolonged, after adjustment for "low-flow" duration, cause of CA and initial rhythm. However, Vaahersalo et al. do not provide "no-flow" durations nor did their study focus on the correct selection of non-shockable patients who could benefit from TH (i.e. those with TH-accessible brain damages) and those who could not (i.e. those with

multiple organ failure leading to early death). Finally, the two groups were small and not comparable [3]. Indeed the aetiologies of the OHCA were different, and the prolonged median time to ROSC in the 70 patients treated with TH (25 min) was significantly higher than in patients without TH. Furthermore, there are still solid arguments in favour of the use of TH in these non-shockable patients. Experimental studies have provided strong data regarding the protective effects of TH in asphyxia and CA models, irrespective of the initial rhythm [5]. Following at least three large indisputable RCTs and five concordant meta-analyses, TH is now recommended in the treatment of neonatal hypoxic-ischaemic encephalopathy because of its beneficial effect on survival and neurological disability [2, 6]. Since 20–25 % of patients with non-shockable CA could finally survive with a favourable neurological outcome at hospital discharge and in the long term [7], it would be interesting to provide TH as the only available treatment to date able to minimize brain damage and long-term disability.

Despite these arguments, nearly all studies including patients with non-shockable CA have shown no effect of TH or a modest benefit in favour of cooling. In a meta-analysis by Kim et al. [8], TH was found to be associated with reduced in-hospital mortality in adults resuscitated from non-shockable CA. However, this effect was not significant regarding the unfavourable neurological outcome on discharge or when the analysis was restricted only to the two small RCTs. Moreover, most of the studies included in the meta-analysis had substantial risks of bias and the quality of evidence was very low. Since the publication of this meta-analysis, several non-randomized studies have shown conflicting results which nourish the controversy [9–12]. Accordingly, a recent Cochrane meta-analysis concluded that the group sizes for patients with asystole or non-cardiac causes of CA were too small to draw firm inferences [13].

The present study by Vaahersalo et al. [3] adds further doubt to the field regarding the likely impact of TH in this subgroup. How could TH have a neutral effect on prognosis in these patients with non-shockable CA? By altering the risk/benefit ratio of this intervention, an increased incidence of TH-related side effects could be an explanation, although not firmly established [7, 13, 14]. In the present study, pneumonia was more frequent in the TH-treated patients—confirming previous data [14, 15]—but this was not related to CA rhythm. The increased length of stay in the TH-treated patients also raises questions about medication associated with hypothermia, since these treatments could delay the evaluation of neurological recovery. Finally, an early use of TH for 24 h targeted to 32–34 °C is the only recommended scheme of treatment in all patients following CA. A modified scheme of targeted temperature management in relation to several factors (optimal TH duration, speed, level, therapeutic window and rewarming) that seem to be of critical importance could be discussed in non-shockable patients considering that the cerebral damages may be more severe [1, 2].

This study clearly contributes to the pro–con debate (Table 1), and underlines the need for a large multicentre study examining the effect of TH in patients with non-shockable OHCA that should include subgroups according to the pathophysiology of the arrest and careful patient selection (Fig. 1). In the meantime, it is now reasonable to discuss on a case-by-case basis the indications for TH in non-shockable patients.

Conflicts of interest None.

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