Alain Cariou
Kjetil Sunde

Cold fluids during cardiac arrest: faster cooling but not better outcome!

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A. Cariou (✉)

Medical Intensive Care Unit, AP-HP, Cochin University Hospital,
27 rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France
e-mail: alain.cariou@cch.aphp.fr

K. Sunde

Surgical Intensive Care Unit Ullevål, Division of Emergencies and
Critical Care, Department of Anaesthesiology, Oslo University
Hospital, Oslo, Norway

In the current issue of *Intensive Care Medicine*, Debaty and coworkers report the results of a very innovative strategy aiming to decrease post-anoxic brain injury [1], which accounts for the vast majority of deaths in patients resuscitated from a cardiac arrest (CA) [2]. Anoxo-ischemic damages are mainly caused by a reperfusion injury called “post-cardiac arrest syndrome” responsible for a cascade of pathophysiological mechanisms that especially damage the brain [3]. This has stimulated intense research (experimental and clinical) over the last 30–40 years aiming to limit the worsening of these neurological lesions occurring during the post-CA period [3], which culminated 10 years ago with the publication of two randomized landmark trials demonstrating that therapeutic hypothermia (TH) post-CA was an effective treatment in getting more neurologically intact survivors [4, 5]. This led to a

rapid change in international recommendations on the management of patients initially surviving CA [6]. Based on clinical evidence, the latest international guidelines recommend that most comatose adult patients with spontaneous circulation after out-of-hospital CA (OHCA) should be cooled to 32–34 °C for 12–24 h [7]. However, a recent very well performed randomized trial (the TTM trial) compared two levels of TH, and found no differences in outcome between 33 and 36 °C [8, 9].

In routine practice, TH is initiated at hospital admission in the emergency department, angiographic laboratory or in the intensive care unit (ICU). Numerous experimental data suggested that a more aggressive approach consisting in a cooling performed as soon as possible after CA could be associated with a greater protective effect [10]. Accordingly, different strategies have been proposed to permit rapid cooling, and intravenous administration of ice-cold fluids is one option that has frequently been investigated in recent years, as this is a simple and easy method. In addition to the cooling effect, controlled in-hospital use of fluids in the early post-resuscitation period is probably important to stabilize the patients, considering the sepsis-like syndrome that is common in these patients [11]. However, in a recent large randomized trial, prehospital rapid infusion of up to 2 L of 4 °C normal saline induced mild hypothermia faster than standard care, but did not improve survival or neurological status at discharge after resuscitation from OHCA [12]. Importantly, the intervention was associated with significantly increased incidence of rearrest during transport, and also time spent in the prehospital setting and pulmonary edema with early diuretic use after admission. So clearly, uncontrolled use of large amounts of fluids in the prehospital setting does not seem to be recommended.

Table 1 Risks and benefits of intra-arrest cooling with cold fluids

Benefits	Risks
Maximal protective effects on brain and other tissues	Decrease in cerebral and coronary perfusion pressure
Myocardial infarct size reduction (if the cause of arrest)	Pulmonary edema and detrimental respiratory consequences
Early volume replacement	Overcooling

Many animal studies have also suggested that the benefit to neurological outcome could be further improved if TH is started during cardiopulmonary resuscitation (CPR), so-called intra-arrest cooling [13]. In a French study, Bruel et al. rapidly cooled 33 CA patients with ice-cold fluids during CPR, and they decreased the body temperature by 2.1 °C after a median of 16 min after return of spontaneous circulation (ROSC) [14]. Considering this was a feasibility study without a control group, the results allowed the design of a larger, multicenter, randomized trial to assess whether prehospital induced cooling after OHCA confers neurological benefits. This led Debaty and coworkers to conduct a 1:1 randomized, multicenter study in three mobile ICUs and four critical care units in France, presented in this issue [1]. In addition to usual care, patients in the intervention group received an infusion of up to 2,000 mL of ice-cold 0.9 % saline solution during OHCA [1]. As the aim of this study was to compare neurological damages following CA, the authors chose the concentration of neuron-specific enolase (NSE), a marker of cerebral injury, at 24 h as primary endpoint, but clinical outcome was also assessed using cerebral performance scores. Intra-arrest cooling decreased the core temperature by an average of 1.7 °C prior to hospital admission and shortened the time to reach 34 °C by an average of 93 min compared to in-hospital TH alone. However, this was not associated with differences in markers of neurological injury or in neurological outcome.

Even if this study was well performed, the results are not surprising considering the low number of initial shockable rhythms in both groups (less than 30 %), the high number of initial asystole (approximately 65 %), more than a median 17 min from call to arrival of advanced life support (ALS), a median 27–30 min from collapse to ROSC and the resulting very low overall survival in both groups (16 % among those admitted with ROSC), indicating that the included patients were too severely injured and not at all comparable to the patients in the HACA trial [5] or the recent TTM trial [8]. This is also confirmed by the lower temperature on admission in the control group than in previous studies [15], higher

NSE values and a high heart rate on admission despite hypothermia [16], all factors associated with worse outcome. Even when started during CPR, TH can definitively not save brains that are already too damaged.

Furthermore the net effect of intra-arrest cooling with fluids also remains questionable for other reasons. Animal studies performed in the 1980s showed that fluid loading during resuscitation reduced both cardiac and cerebral blood flow, as a result of the increased right atrial and intracerebral pressures [17]. In 2009 Yannopoulos et al. [18] also showed that cold saline altered coronary perfusion pressure. All these findings suggest that intra-arrest cooling with large amounts of cold fluids might be more detrimental than beneficial during CPR (Table 1). If intra-arrest cooling is to be further explored, other methods should probably be preferred. To date, several possibilities are in development. In a rabbit model of cardiac arrest, total liquid ventilation (TLV) with temperature-controlled perfluorocarbons has been shown to induce a very rapid and generalized cooling. This “ultrafast cooling” exerts potent neurological and cardiac protection and could be a relevant approach to provide a global and protective hypothermia against the post-cardiac arrest syndrome [19]. Another approach consists in using transnasal evaporative cooling, which has sufficient heat transfer capacity for effective intra-arrest cooling in animal models. This method allows cooling to be initiated within minutes of the arrest and has been shown to cool the brain before circulation is reestablished. In humans, the system has been tested in a randomized field study, which showed promising results regarding feasibility and effectiveness in accelerating the cooling process [20]. A multicenter, prospective study is currently recruiting to explore its ability to improve outcome (NCT01400373).

Finally, several questions remain unanswered: considering that TH or targeted temperature management is useful, what temperature should be targeted and when should it start? The complexity and specific pathophysiology of cardiac arrest with different degrees of reperfusion injury indicate that it is probably not a “one size fits all” strategy, making research on this group of patients even more challenging.

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