Editorial

Targeted temperature management after cardiac arrest: the longer, the better?

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Despite recent improvements in their management, the prognosis of patients resuscitated from an out-of-hospital cardiac arrest (OHCA) remains poor, as reflected by a very high mortality rate (1-3). In patients in whom a return of spontaneous circulation (ROSC) has been obtained due to cardiopulmonary resuscitation (CPR), many subsequent deaths are observed during the following days and weeks, most of these deaths resulting from anoxic-ischemic brain damages (4). The pathophysiology of neurological injury observed in this setting involves both direct ischemic damages and reperfusion injury. In this setting, induced hypothermia is employed for many years since this treatment may reduce tissue metabolism and cerebral oxygen consumption, and may also decrease the burst oxidative process and the activation of different detrimental pathways (5). Two randomized controlled trials have been performed in the early 2000s (6,7), both reporting a clinical benefit of mild therapeutic hypothermia (between 32 and 34 ℃) in comatose patients after cardiac arrest. In the following decade, many observational studies also reported a better outcome in patients managed with induced hypothermia. Considering these consisting results, international guidelines recommend to induce a mild hypothermia in all patients successfully resuscitated from an OHCA, providing that they remain comatose after ROSC (8,9).

Even if induced hypothermia is recommended in post-cardiac arrest patients, optimal modalities of the temperature management are still debated. The level of temperature has been questioned in a large trial from Nielsen *et al.*, in which no significant differences in outcome was observed by targeting 33 or 36 ℃ (10). Consistent results have been recently reported in both in-hospital cardiac arrest in adults (11) and children (12). Consequently, European and American 2015 guidelines advocate to maintain a constant, target temperature between 32 and 36 ℃ for those patients (8,9) and several clinical studies are on the way in order to test some alternatives. Regarding the optimal duration of induced hypothermia, European and American 2015 guidelines suggested to lower the body temperature for at least 24 hours, and then to avoid fever for at least 72 hours. However this recommendation regarding the optimal duration of induced hypothermia was weak and it was based on a very low quality evidence (8). Indeed, when these guidelines were elaborated, the potential benefit of using a longer duration of targeted temperature management (TTM) has never been clinically evaluated, even if it was supported by experimental findings (9). In small animal experiments, histologic assessment of neuronal survival revealed a potentially greater neuroprotection when therapeutic hypothermia was maintained for 48 as compared with 24 hours (13). In larger animals (pigs), searchers found that 48 hours of therapeutic hypothermia was more effective

in attenuating brain apoptosis than 24 hours of therapeutic hypothermia (14). In humans with OHCA, this approach was supported only by retrospective data from small cohort studies. In a small number of patients with ROSC after pulseless electrical activity/asystole or prolonged ventricular fibrillation, it was shown that a prolonged hypothermia (72 hours) may blunt the inflammatory response after rewarming in patients after cardiac arrest (15). Because inflammation is a strong mediator of secondary brain injury, this observation also suggested that a prolonged hypothermia may be beneficial. However, in a retrospective study, Kagawa and coll. reported that prolonged durations of cooling and rewarming was not associated with an improved outcome and may increase complications (16).

To address this issue, a recent study by Kirkegaard and coll. compared standard duration of induced hypothermia (24-hour group) to a longer duration (48-hour group) (17). In this international, multicenter, randomized trial, 355 comatose patients with ROSC after OHCA were randomized to undergo induced hypothermia, either during 24 or 48 hours. A strict protocol of temperature management was applied, with maintenance of targeted temperature (33 ℃) for either 24 or 48 hours according to randomization, and thereafter rewarming with temperature control aiming 37 ℃. According to the most recent guidelines, a stringent protocol regarding neurologic prognostication was applied for all patients remaining comatose, using a multimodal approach. The main endpoint was the recovery of brain function as attested by a Cerebral Performance Categories (CPC) level of 1 or 2 at 6 months after OHCA.

Strict inclusion criteria led to include a selected population, mostly male (80%) with an initial shockable rhythm in 90% of patients, and with a bystander-CPR in more than 80% of patients. Patients were managed according to current standards of care, with immediate coronary angiogram in over 80% of patients, and all patients were mechanically ventilated. Induced hypothermia was applied using internal or external methods, and time to reach the target temperature was shorter in the 48-hour group (4.6 *vs.* 5.3 hours in the 24-hour group), without significant impact in subgroup analysis. Regarding protocol violations, 6% of patients in 48-hour group had rewarming earlier than expected, as compared with 2% in 24-hour group. During follow-up, 64% of patients in the 24-hour group met the primary outcome (CPC score 1 or 2 at 6 months), as compared with 69% of patients in 48-hour group. This 5% difference did not reached statistical significance (RR =1.08, P=0.33). Similarly, authors reported a non-significative trend towards a lower 6-month mortality (27% in 48-hour group as compared with 34% in 24-hour group, P=0.19). Results were consistent across predefined subgroups, and there was no benefit in the 48-hour group regarding secondary outcomes. As expected, duration of mechanical ventilation and ICU length of stay were significantly longer in the 48-hour group, but rates of pneumonia and bleeding did not differ. Interestingly, the intervention was stopped early in 6% of the patients in the 48-hour group and 2% in the 24-hour group, a difference that was statistically significant and may reflect how it is difficult to maintain the hypothermia over a long period.

As underlined by authors, this pragmatic study could have been underpowered to detect meaningful difference. Indeed, authors hypothesized a 50% rate of favorable outcome in the 24-hour group, based on data previously published. However, probably because of a selection bias, the rate of favorable neurologic outcome was higher than expected (64% in the control group, *vs.* 50% planned in the power calculation). Moreover, authors calculated their estimated sample size considering a 15% absolute difference being a meaningful difference (according to previous studies). The 5%-difference that was observed, although statistically non-significant, might be considered as a clinically relevant difference. However, testing such a small difference in this setting would require inclusion of 3,000 patients. Moreover, ICU physicians were not blinded to randomization group, for obvious pragmatic reasons and that may be another bias.

Even if the results are negative, Kirkegaard and coll. must be congratulated as they performed an elegant study that provides another brick in the wall of therapeutic hypothermia after cardiac arrest. Accordingly to the main result, a longer duration (i.e., 48 hours instead of 24 hours) of hypothermia cannot be recommended as a standard of care nowadays. After Nielsen *et al.* questioning the target temperature (10), and several other negative studies exploring different settings, the present study highlights how further clinical research is necessary in order to refine temperature management modalities after cardiac arrest. TTM is a time-consuming care and several upcoming studies, including the TTM-2 trial (hypothermia versus "just avoiding fever" after OHCA, NCT 02908308) and the HYPERION trial (hypothermia versus normothermia in non-shockable OHCA, NCT 01994772) (18) will hopefully provide important data that will clarify modalities, objectives and population for TTM after OHCA.

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Footnote

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