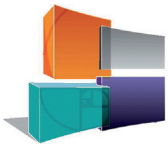
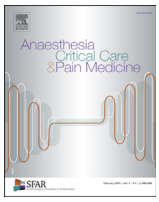
Anaesth Crit Care Pain Med 38 (2019) 573–574



SFAR
Société Française d'Anesthésie et de Réanimation



Editorial

Therapeutic hypothermia after cardiac arrest: We have found the missing piece puzzle!

ARTICLE INFO

Keywords:
Cardiac arrest
Targeted temperature management
Outcome

The influence of temperature on different conditions has been described since Hippocrates. In the last century, Benson reported a favourable outcome after cardiac arrest with the use of hypothermia [1]. Later, several reports highlighted the deleterious effects of hyperthermia in several conditions, and especially after cardiac arrest [2,3]. After decades of being neglected, therapeutic hypothermia has returned to the forefront at the beginning of the 21st century. In 2002, two studies reported an improved neurological outcome with the use of therapeutic hypothermia compared to normothermia in patient presenting an initial shockable rhythm [4,5]. However, a significant percentage of patients in the control group of the HACA study developed fever; it was therefore unclear if the benefits resulted from hypothermia or the avoidance of hyperthermia. To answer this question, the large prospective TTM study compared the targeted temperatures of 33 *vs.* 36 °C in patients with an out-of-hospital cardiac arrest from a presumed cardiac cause [6]. In both groups, the temperature was controlled during the interventions, introducing the concept of targeted temperature management instead of therapeutic hypothermia. Contrary to previous studies, the authors did not show any benefit of hypothermia compared to normothermia. This led the ILCOR to modify its guidelines concerning temperature from 32–34 °C to a targeted temperature management of 32–36 °C, for all patients with coma following cardiac arrest [7]. However, the generalisation of these guidelines is questionable. Most studies supporting these recommendations included cardiac arrest patients presenting an initial shockable rhythm. But the level of evidence for patients presenting an initial non-shockable rhythm remains poor, despite their high proportion in the cardiac arrest population and their unfavourable outcome. Moreover, these studies reported conflicting results. Indeed, a retrospective non-randomised study showed an improved neurological outcome associated with therapeutic hypothermia 32–34 °C [8], while a secondary analysis of the non-shockable rhythm patients included in the TTM study did not show a difference between targeted hypothermia and targeted normothermia. Thus, there was a need for a randomised trial assessing therapeutic hypothermia in survivors of cardiac arrest with an initial non-shockable rhythm.

In a recent prospective multicentric trial, Lascarrou et al. compared two different strategies of temperature management in out-of-hospital and in-hospital cardiac arrest patients presenting a non-shockable rhythm (asystole and pulseless electrical activity) [9]. In the moderate therapeutic hypothermia arm, patients were cooled, maintained at 33 ± 0.5 °C for 24 hours and rewarmed gradually to 37 ± 0.5 °C for 24 hours. In the controlled normothermia arm, patients were maintained actively to a temperature of 37 ± 0.5 °C during 48 hours. The neurological outcome was assessed by the cerebral performance category scale on day 90. The results showed an improved survival with favourable neurologic outcome (cerebral performance category 1 and 2) in the group treated with moderate therapeutic hypothermia compared to the targeted normothermia group reaching 10.2% *vs.* 5.7%; $P = 0.04$. The mortality at day 90 was mainly due to the withdrawal of life-sustaining treatments, comparable in both groups. Across subgroups, the results of the intervention seemed consistent. The percentages of potential complications attributable to hypothermia (arrhythmia, infections) were not different between groups. Unfortunately, we can regret the lack of data on the proportion of patients in the target temperature during the intervention, as well as for the percentage of fever. A recent work showed a dramatic increase of this proportion after the change of target temperature from hypothermia to normothermia [10]. This is even more important as the study reports a seemingly higher percentage of use of basic external cooling in the normothermia group. The intravascular cooling catheter and the surface closed-loop devices are not associated to a better outcome, but allow a better temperature management [11].

The authors should be congratulated for this study of paramount importance. Aside from representing the first randomised trial of temperature intervention in non-shockable rhythm cardiac arrest patients, it also showed an improvement in neurologic outcome. However, these positive results favouring therapeutic hypothermia compared to normothermia add complexity in the temperature management of these patients. On one hand, it supports the ILCOR guidelines with high quality data for the target temperature 32–36 °C. On the other hand, it does not

https://doi.org/10.1016/j.accpm.2019.10.008

support the assertion that hypothermia and normothermia are equally good or bad. The ILCOR guidelines cover a large range of target temperature from hypothermia to normothermia. Knowing the effects of temperature on homeostasis, these guidelines actually offer very different treatments. These interventions might act differently according to the patients' characteristics and the circumstances of cardiac arrest (in-hospital *vs.* out-of-hospital, shockable *vs.* non-shockable rhythm). Therapeutic hypothermia can thus be beneficial in non-shockable rhythm [9], neutral in shockable rhythm [6] and deleterious in in-hospital cardiac arrest [12]. These discrepancies argue for adapting target temperature according to criteria that remains to be determined.

In summary, the HYPERION trial fills a major gap in the care of post-cardiac arrest patients presenting an initial non-shockable rhythm suggesting that therapeutic hypothermia improves neurological outcome.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Benson DW, Williams GR, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. Anesth Analg 1959;38:423–8.
[2] Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, Havel C, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001;161:2007–12.
[3] Bro-Jeppesen J, Hassager C, Wanscher M, Søholm H, Thomsen JH, Lippert FK, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. Resuscitation 2013;84:1734–40.
[4] Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.
[5] Hypothermia after Cardiac Arrest Study Group.. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
[6] Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted Temperature management at 33 °C versus 36 °C after cardiac arrest. N Engl J Med 2013;369:2197–206.
[7] Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VRM, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:202–22.
[8] Testori C, Sterz F, Behringer W, Haugk M, Uray T, Zeiner A, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. Resuscitation 2011;82:1162–7.
[9] Lascarrou J-B, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med 2019. NEJMoa1906661-11. [Epub ahead of print].
[10] Bray JE, Stub D, Bloom JE, Segan L, Mitra B, Smith K, et al. Changing target temperature from 33 °C to 36 °C in the ICU management of out-of-hospital cardiac arrest: a before and after study. Resuscitation 2017;113:39–43.
[11] Deye N, Cariou A, Girardie P, Pichon N, Megarbane B. Endovascular versus external targeted temperature management for patients with out-of-hospital cardiac arrest. Circulation 2015;132:182–93.
[12] Chan PS, Berg RA, Tang Y, Curtis LH, Spertus JA. for the American Heart Association's Get With The Guidelines-Resuscitation Investigators. Association between therapeutic hypothermia and survival after in-hospital cardiac arrest. JAMA 2016;316:1375–417.

Romain Rozier, Vincent Bruckert, Jean-Christophe Orban*
Pôle Anesthésie Réanimations Urgences, Centre Hospitalier Universitaire de Nice, 30 Voie Romaine, 06006 Nice, France

*Corresponding author
E-mail address: orban.jc@chu-nice.fr (J.-C. Orban).