

## Reply to: Therapeutic hypothermia after cardiac arrest: outcome predictors

*Resposta para: Hipotermia terapêutica após parada cardíaca: preditores de prognóstico*

We would like to thank the interest paid to our study and the valuable comments regarding it.<sup>(1)</sup> Herein, we clarify the comments and questions raised.

Despite advances in cardiopulmonary resuscitation, cardiac arrest is still associated with high morbidity and mortality.<sup>(2)</sup> Survival of these patients depends on the quality of care, and despite the fact that basic and advanced life support have been the subject of intensive research, the main focus is currently on care provided post-recovery of spontaneous circulation.<sup>(3)</sup> Therapeutic hypothermia has been shown to be effective in the prevention and reversal of neurological injury, cardiac protection, and mortality reduction.<sup>(4)</sup> It has been recommended since 2003 in comatose outpatients with ventricular fibrillation. Subsequent studies have shown the benefits of its immediate use after spontaneous circulation is restored and with other initial rhythms, which led to the initiation of cooling in pre-hospital settings and in patients with other rhythms.<sup>(5,6)</sup> This fact introduced a new variable in the so important prognosis evaluation of patients; thereby, we conducted a study to determine the validity of several markers that could be used to identify patients with poor prognosis who underwent therapeutic hypothermia after cardiac arrest. Thus, we studied the influences of the setting (in-hospital and out-of-hospital), time, rhythms, clinical evaluation, and biochemical, neurophysiological or imaging parameters on the final prognosis, using a population that was appropriate for these analyses.

In regard to the discussion, we agree with the observation that the initial temperature was not presented. We chose not to include the initial temperatures in the study because this parameter was not collected in a systematic manner, which could then bias the results. Nevertheless, we found that the initial temperatures of the patients ranged from 35.5°C to 36.8°C. Similarly to Perman et al., we observed that patients who reached the target temperature faster had worse prognosis.<sup>(7)</sup> We hypothesized that this was due to the existence of more extensive and irreversible neurological damage, which would make the patient less reactive to temperature decrease, with fewer tremors and reduced need for sedation, thus allowing faster cooling.<sup>(8)</sup> In fact, this hypothesis implies that the lower reactivity to temperature decrease may be a secondary prognostic factor for more severe neurological injury and, consequently, may determine a shorter time for the target temperature to be reached, consistent with the results of our study, with all the variables interconnected.<sup>(7-10)</sup>

As already mentioned, some studies suggest that the early onset of therapeutic hypothermia after cardiac arrest is a safe and beneficial treatment to reduce mortality and improve neurological outcomes, and this has led to

its establishment in the pre-hospital setting. In our study, there was no improvement of the prognosis when the protocol was subjected to pre-hospital initiation, which is consistent with the results of several investigations.<sup>(9-13)</sup> As for the study by Kim et al., the authors concluded that induction of pre-hospital hypothermia increased the time that the patient spent in the pre-hospital setting, the number of re-arrests that occurred during transport, and the occurrence of acute pulmonary edema, in addition to possibly delaying the implementation of interventions such as cardiac catheterization.<sup>(11)</sup> In our study, pre-hospital induction of hypothermia did not delay patient admission to our unit nor the implementation of coronarography, which was performed within 12 hours, as recommended by the European Society of Cardiology.<sup>(14)</sup> Moreover, there were no cardiac arrests during transport or episodes of acute pulmonary edema. We also clarified that no patients included in the study experienced therapeutic limitation or withdrawal of support.

Recent studies, such as that by Nielsen et al., suggest that avoiding hyperthermia can be as beneficial as hypothermia.<sup>(15)</sup> These data led to changes in the recommendations of the American Heart Association and the European Resuscitation Council, which then suggested a more liberal approach, allowing temperatures between 32 - 36°C, according to the patient's case.<sup>(16)</sup> We believe that the fact that we did not compare the temperature level with mortality and neurological outcomes represents a limitation that was not previously considered as the study was designed and initiated prior to the publication of the study by Nielsen et al. accordingly with the existing recommendations at the time.

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## REFERENCES

1. Leao RN, Avila P, Cavaco R, Germano N, Bento L. Therapeutic hypothermia after cardiac arrest: outcome predictors. *Rev Bras Ter Intensiva.* 2015;27(4):322-32.
2. Deasy C, Bray JE, Smith K, Wolfe R, Harriss LR, Bernard SA, et al. Cardiac arrest outcomes before and after the 2005 resuscitation guidelines implementation: evidence of improvement? *Resuscitation.* 2011;82(8):984-8.
3. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. *Ann Neurol.* 2010;67(3):301-7.
4. Moore EM, Nichol AD, Bernard SA, Bellomo R. Therapeutic hypothermia: benefits, mechanisms and potential clinical applications in neurological, cardiac and kidney injury. *Injury.* 2011;42(9):843-54.
5. 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(8):557-63.
6. Deakin CD, Morrison LJ, Morley PT, Callaway CW, Kerber RE, Kronick SL, Lavonas EJ, Link MS, Neumar RW, Otto CW, Parr M, Shuster M, Sunde K, Peberdy MA, Tang W, Hoek TL, Böttiger BW, Drajer S, Lim SH, Nolan JP; Advanced Life Support Chapter Collaborators. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation.* 2010;81 Suppl 1:e93-e174.
7. Perman SM, Ellenberg JH, Grossestreuer AV, Gaieski DF, Leary M, Abella BS, et al. Shorter time to target temperature is associated with poor neurologic outcome in post-arrest patients treated with targeted temperature management. *Resuscitation.* 2015;88:114-9.
8. Nair SU, Lundbye JB. The occurrence of shivering in cardiac arrest survivors undergoing therapeutic hypothermia is associated with a good neurologic outcome. *Resuscitation.* 2013;84(5):626-9.
9. Benz-Woerner J, Delodder F, Benz R, Cueni-Villoz N, Feihl F, Rossetti AO, et al. Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia. *Resuscitation.* 2012;83(3):338-42.
10. Haugk M, Testori C, Sterz F, Uranitsch M, Holzer M, Behringer W, Herkner H; Time to Target Temperature Study Group. Relationship between time to target temperature and outcome in patients treated with therapeutic hypothermia after cardiac arrest. *Crit Care.* 2011;15(2):R101.
11. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA.* 2014;311(1):45-52.
12. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, Kelly AM, Silvester W; Rapid Infusion of Cold Hartmanns (RICH) Investigators. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation.* 2010;122(7):737-42.
13. Italian Cooling Experience (ICE) Study G. Early- versus late-initiation of therapeutic hypothermia after cardiac arrest: preliminary observations from the experience of 17 Italian intensive care units. *Resuscitation.* 2012;83(7):823-8.
14. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33(20):2569-619.
15. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammed P, Wanscher M, Wise MP, Åneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lijla G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med.* 2013;369(23):2197-206.
16. Nolan JP, Soar J, Cariou A, Cronberg T, Moulart VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med.* 2015;41(12), 2039-56. Erratum in: *European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care.* [Intensive Care Med. 2016].