

Reply to: Neurological outcome after cardiac arrest: cold and dark issues [editorial]

Resposta para: Desfecho neurológico após parada cardíaca: problemas frios e sombrios [editorial]

We are thankful for the interest in our editorial.⁽¹⁾ We agree that the study population in Kim et al.⁽²⁾ is different from that of Leão et al.⁽³⁾, insofar as the first consisted of patients who had pre-hospital cardiorespiratory arrest, and the second consisted of patients with out-of-hospital and in-hospital cardiorespiratory arrest. However, neither study showed benefits to achieving the target hypothermia more quickly. In addition, the study by Leão et al. suggested a worse prognosis in patients who reached hypothermia more quickly.⁽³⁾ As mentioned in the editorial, although the study had several limitations, there is a pathophysiological rationale for this finding.^(4,5)

Obviously, we agree that the study of Leão et al.⁽³⁾ did not aim to assess the impact of temperature control. However, by showing that reaching hypothermia early was associated with worse neurological outcomes, the study adds to other recent evidence questioning the use of this therapeutic strategy.^(2,6) It is important to highlight that the two major studies in which the recommendation to apply hypothermia after spontaneous circulation is restored compared hypothermia with no intervention on the patients' temperature.^(7,8) In both studies, the control group had a core temperature above 37.5°C in the first 24 hours after recovery of spontaneous circulation. An important issue associated with these studies is that it is known that early hyperthermia after restoration of spontaneous circulation is associated with worse prognosis.⁽⁹⁾ Thus, the better outcomes associated with hypothermia may merely be a consequence of temperature control and not of the hypothermia itself in the intervention groups. The study by Nielsen et al. shows that this assumption may be true, as normothermia (36°C) led to results similar to hypothermia (33°C) in regards to mortality, neurological deficits⁽⁶⁾, and quality of life.⁽¹⁰⁾ Moreover, one of the studies mentioned above should be considered "quasi-randomized" considering the methodology employed.⁽⁸⁾

In addition to the evidence provided in the study by Nielsen et al.⁽⁶⁾, which showed no superiority of hypothermia in relation to normothermia, we believe that there are two obstacles for the indiscriminate adoption of hypothermia after cardiorespiratory arrest. First, the induction of hypothermia with infusion of cold saline solution, perhaps the most widely available method in our setting, is associated with increased risk of pulmonary edema,⁽²⁾ which could be a serious problem for patients with heart or kidney failure. Second, hypothermia is not exempt from complications, which include electrolyte disorders (hypokalemia, hypomagnesemia, and hypophosphatemia)⁽¹¹⁾ and increased risk of infection.^(7,11,12) Based on these assumptions, we believe (for the time

being and until further evidence is provided) that a core temperature of 36°C is a more viable option in our setting.

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REFERENCES

1. Granja C, Nassar Junior AP. Neurological outcome after cardiac arrest: cold and dark issues [editorial]. *Rev Bras Ter Intensiva*. 2015;27(4):305-6.
2. 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.
3. 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.
4. Yannopoulos D, Zviman M, Castro V, Kolandaivelu A, Ranjan R, Wilson RF, et al. Intra-cardiopulmonary resuscitation hypothermia with and without volume loading in an ischemic model of cardiac arrest. *Circulation*. 2009;120(14):1426-35.
5. 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.
6. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet 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, Lilja 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.
7. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-56. Erratum in *N Engl J Med* 2002;346(22):1756.
8. 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.
9. Gebhardt K, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC; Post Cardiac Arrest Service. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. *Resuscitation*. 2013;84(8):1062-7.
10. Cronberg T, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, Hovdenes J, Gasche Y, Åneman A, Stammet P, Erlinge D, Friberg H, Hassager C, Kuiper M, Wanscher M, Bosch F, Cranshaw J, Kleger GR, Persson S, Undén J, Walden A, Winkel P, Wetterslev J, Nielsen N; TTM Trial Investigators. Neurologic function and health-related quality of life in patients following targeted temperature management at 33°C vs 36°C after out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA Neurol*. 2015;72(6):634-41.
11. Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, Valsson F, Wanscher M, Friberg H; Hypothermia Network. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand*. 2009;53(7):926-34.
12. Perbet S, Mongardon N, Dumas F, Bruel C, Lemiale V, Mourvillier B, et al. Early-onset pneumonia after cardiac arrest: characteristics, risk factors and influence on prognosis. *Am J Respir Crit Care Med*. 2011;184(9):1048-54.