

Does temperature management improve outcome in patients resuscitated from a non-shockable rhythm?

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Comment on: Sung G, Bosson N, Kaji AH, *et al.* Therapeutic Hypothermia After Resuscitation From a Non-Shockable Rhythm Improves Outcomes in a Regionalized System of Cardiac Arrest Care. *Neurocrit Care* 2016;24:90-6.

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Background

Therapeutic hypothermia or targeted temperature management (TTM) has in the last 15 years been widely implemented (1) as a means to ameliorate the systemic inflammatory response often seen in comatose patients resuscitated from out-of-hospital cardiac arrest (OHCA), later defined as the post cardiac arrest syndrome (PCAS). The PCAS includes anoxic brain injury, myocardial dysfunction and systemic is chemia/reperfusion injuries caused by the arrest itself and/or the precipitating cause of the arrest (2). The treatment modality of TTM was introduced in humans by two prospective randomized trials from 2002 targeting a core temperature of 32–34 °C (3,4), including a combined total of 352 patients, finding favorable neurological outcome in patients treated with TTM. These studies included patients resuscitated from a shockable rhythm [ventricular tachycardia (VT) and/or ventricular fibrillation (VF)], whereas patients resuscitated from a non-shockable rhythm [pulseless electrical activity (PEA) and asystole] were not assessed for inclusion.

The International Liaison Committee on Resuscitation swiftly in 2003 published an advisory statement recommending TTM for patients remaining comatose after OHCA resuscitated from VF (level of evidence 1), while acknowledging that the treatment for patients resuscitated from other causes and rhythms were only supported by level 4 evidence (5). Later, the international multicenter TTM-

trial was conducted randomizing 939 comatose survivors of OHCA to TTM at 33 *vs.* 36 °C (6). Included patients with data on initial rhythm were resuscitated from both shockable (n=729) and non-shockable rhythm (n=178). The results of the TTM-trial demonstrated similar mortality and neurological outcome between the two temperature strata, both combined and stratified by initial rhythm (7). As of now no randomized trials of TTM *vs.* no temperature management in non-shockable patients have been performed or published. The recent 2015 guidelines from the European Resuscitation Council do support TTM for patients with a non-shockable rhythm, but only as a weak recommendation based on very low level of evidence (8). A clinical prospective trial (IL-HYPERION NCT02711098) randomizing comatose survivors of OHCA for TTM *vs.* normothermia was however commenced May 2016, with on-going patient inclusion.

TTM for patients resuscitated from a non-shockable rhythm

Sung *et al.* (9) used a retrospective database based on an emergency medical system (EMS) in a large metropolitan area to shed light on the effects of utilization of TTM for neuro-protection in patients resuscitated from OHCA with an initial non-shockable rhythm (PEA, asystole and AED advise not to shock). All 1,432 patients were transported to centres with implemented TTM protocols, while the

decision to induce hypothermia at 32–34 °C, was guided by institutional policies and finally at the discretion of the treating physician. In-hospital mortality and neurological outcome were reported to a centralized database. TTM was induced in 42% of the included patients, with a survival rate with good neurological outcome of 14% compared to 5% in patients not receiving TTM. The association of favorable outcome with TTM remained in multivariable analysis adjusted for age, witnessed arrest, bystander CPR, rhythm, catheterization, PCI, vasopressor support. A propensity score for likelihood of receiving TTM was used to adjust for large differences between the groups with unchanged results. However, the TTM group was 5 years younger (68 *vs.* 73 years old), more often male (60% *vs.* 53%), more often had witnessed arrest (85% *vs.* 79%) and with higher usage of defibrillation at any time during resuscitation (27% *vs.* 20%). Further catheterization and primary coronary intervention (6% *vs.* 1%) was performed more often in TTM treated patients.

While the authors should be commended on a well-performed epidemiological study, we believe the conclusions drawn from this study are not fully supported by the data. The title and the discussion lead with the sentence “In the LA County regional system for OHCA care, TH improved overall survival and survival with good neurologic outcome in patients resuscitated from cardiac arrest with an initial non-shockable rhythm”. This postulate indicates a causal relation between TTM and favorable outcome in this population, which cannot be drawn from a retrospective observational study. The authors do modify their statement as an association in the conclusion and acknowledge the risk of selection bias, but several potential sources of bias remain including the lack of available data on time to return of spontaneous circulation and reason for withheld TTM in one third of the patient cohort. The authors further excluded variables in the adjusted analysis with documented baseline differences between TTM treated patients and untreated patients, including gender and defibrillation at any time during resuscitation. Both have been shown to influence outcome after OHCA (10,11). A recent review of utilisation of TTM for patients with non-shockable rhythm conclude that further studies are needed to identify which patients may benefit for the treatment (12). In terms of selection bias, evidence suggests that the level of care indeed matters with higher survival rates following OHCA at tertiary heart centres with e.g., available intensive care, coronary interventions and pacemaker-implantation (13).

Perspectives

The study of Sung *et al.* (9) is important with regards to characterising the patients we as treating physicians choose for intensive post cardiac arrest care including TTM and the patients we choose not to treat. The study also document possible adverse events including infections, bleeding complications, dysrhythmia and electrolyte derangement in TTM treated patients. Due to the inherent bias of retrospective observations, we refrain from concluding on any causality between the treatment modality and favorable outcome in patients resuscitated from a non-shockable rhythm. A large and well-powered randomized study (TTM *vs.* no temperature management in non-shockable OHCA patients) with a protocolled plan for other parts of post cardiac arrest care is needed to establish the lacking evidence in this area. So, to answer the title of this commentary “Does temperature management really improve outcome in patients resuscitated from a non-shockable rhythm?”. We simply don’t know yet, but support any efforts in elucidating this important area without jumping to conclusions.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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