REVIEWS

Dillemas in the use of therapeutic hypothermia after cardiac arrest

Doron Zahger

BACKGROUND

Sudden cardiac death is a leading cause for mortality and severe disability worldwide. Survival following out of hospital cardiac arrest remains very low, in the range of 5-10%[1] and many survivors are left with significant neurological impairment. Most patient who die after out of hospital cardiac arrest die as a direct consequence of the neurological insult.

Hypothermia has long been known to be associated with better outcome following drowning and was used to protect the brain during cardiac and brain surgery. In 2002 two pivotal trials were published which demonstrated the ability of mild therapeutic hypothermia (MTH) to improve survival and neurological outcome following out of hospital cardiac arrest[2,3]. Since then, MTH was recommended by the resuscitation guidelines and adopted in many centers. However, important questions remain concerning the use of this modality in real practice. This brief review highlights the main current dilemmas in the field.

THE PIVOTAL TRIALS

The European HACA investigators randomized 275 patients with out of hospital cardiac arrest due to ventricular fibrillation (VF) to either MTH or standard treatment. Cooling was achieved in hospital by means of ice packs and cooling blankets and treatment was given for 24 hours. Bernard and co workers from Australia randomized 77 survivors of out of hospital VF to MTH or standard treatment. Cooling was started pre hospital and achieved by ice packs. In both trials the experimental arm involved cooling to 32-34 degrees. The HACA trial showed a significant reduction in mortality and neurological disability in the MTH arm. The smaller Australian trial could only show improved neurological outcome. A meta analysis of the randomized trials showed a significant 68% increase in the rate of survival with favorable neurological outcome at hospital discharge[4].

QUESTION 1: Should MTH be applied regardless of initial rhythm?

Both seminal trials which examined the role of MTH following cardiac arrest included only patients whose initial rhythm was VF. It is well documented that patients with non shockable rhythms on presentation have a much worse prognosis than patients presenting in VF, probably reflecting a longer time to initiation of resuscitation and/or more profound myocardial damage[5]. A number of registries examined the role of this treatment among patient initially presenting with non shockable rhythms (asystole or pulseless electrical activity). In a large French registry Dumas et al. compared the effects of MTH among patients who presented with VF or with a non shockable rhythm[6]. Among 1145 patients admitted after out of hospital cardiac arrest 457 received MTH after an initial shockable rhythm. Of those, 44% had a favorable neurological outcome compared to just 15% of patients who received MTH after presenting with a non shockable rhythm. In a multivariate analysis MTH predicted better outcome only among patients presenting with a shockable rhythm but seemed ineffective among others. Sandroni al performed a meta analysis of all studies which examined the effect of MTH after non VT/VF cardiac arrest[7]. Their results showed a very small, but significant benefit of treatment in this population. However, the quality of the data was very poor and was based mostly on observational data.

In summary: MTH does not seem harmful in patients who initially presented with a non shockable rhythm. The prognosis of these patients is very poor

[1] Soroka University Medical Center Faculty of Health Sciences, Ben Gurion University of the Negev

Contact address:
Doron Zahger, MD
Department of Cardiology, Soroka University Medical Center
Faculty of Health Sciences, Ben Gurion University of the Negev
Beer Sheva, Israel. Email: dzahger@bgu.ac.il

and might be improved very slightly with MTH. Until larger randomized trials are available the decision regarding MTH should be individualized based on all relevant factors such as the patient's age, time to initiation of CPR, time to return of spontaneous circulation and neurological status on admission. Current guidelines provide similar recommendations.

QUESTION 2: Should MTH be started pre hospital?

As mentioned above, the Australian study used pre hospital cooling while in the European trial cooling was initiated in the Emergency Department. Pre hospital cooling is logistically challenging but animal data suggest earlier cooling may improve outcome. Wolff et al.[8] examined the relation between time to achievement of target temperature and outcome and showed that neurological outcomes were better among those patients in whom target temperatures were achieved faster. Bernard and co-workers randomized 234 patients after cardiac arrest to pre hospital or in hospital cooling[9]. Neurological outcomes did not differ significantly between groups. Similarly, a meta analysis of all studies available until 2013 failed to show an effect of pre hospital cooling on survival after cardiac arrest as compared to in hospital cooling[10]. Finally, Kim et al randomized 1364 survivors of out of hospital cardiac arrest to pre hospital or in hospital cooling and could not demonstrate any beneficial effect of the earlier intervention, even though core temperature was reduced earlier in the intervention group[11].

In summary: there is no justification to routinely initiate MTH in the pre hospital cooling, especially considering the substantial logistical difficulties involved. Whether such intervention might be justified when evacuation times are very prolonged remains to be determined.

QUESTION 3: What should the target temperature be?

The initial trials of MTH compared cooling to 32-34 degrees Celsius to no cooling. More recently, the Targeted Temperature Management trial randomized 939 patient after out of hospital cardiac arrest to receive either cooling to 32-34 degrees or to a milder form of temperature control of 36 degrees[12]. To the surprise of many, despite the achieved difference in body temperature according to the protocol no significant differences were found in survival or neurological outcome between groups. The reasons for this surprising finding are incompletely understood. First, it is important to realize that the experimental arm in this study included a mild form of temperature control and is not the equivalent of no cooling. Conceivably, it might be more important to prevent hyperthermia, which is common after cardiac arrest, than to induce hypothermia. Another important might be the fact that in this study the median time to initiation of bystander CPR was only 1 minute. This very fast response might have resulted in a generally better neurological outcome and it might therefore have been harder to show an effect of hypothermia. However, the time to return of spontaneous circulation in this trial was about 25 minutes, similar to the initial studies of MTH. Furthermore, this study of 939 patients is much larger than all previous studies combined and its results appear robust. Following this study ILCOR has issued a statement that until more thorough review of the data is performed clinicians should adhere to the previous recommendation (i.e. cooling to 32-34 degrees) but the committee recognized that some clinicians may choose to follow the milder form of temperature controlled suggested by this trial.

In summary: The results of the TTM trial justify using a milder protocol of hypothermia, as done in this trial. Whether patients with longer delays to initiation of bystander CPR might benefit from more profound cooling remains to be seen.

SUMMARY

The key to improve survival after out of hospital cardiac arrest is rapid CPR and defibrillation. MTH has an important role in minimizing neurological outcomes and improving survival. Cooling should be started in comatose patients initially presenting with VF or pulseless VT while the benefit among patients with an initially non shockable rhythm is questionable. MTH should generally be instituted in hospital. Good evidence supports a target temperature of 36 degrees as done in the TTM trial. Ongoing trials are expected to clarify further these critical questions in the application of MTH after cardiac arrest.

Conflict of interest: none declared

References

1. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010 Nov;81(11):1479-87
2. The Hypothermia after Cardiac Arrest Study Group. Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. N Engl J Med 2002; 346:549-556.
3. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. N Engl J Med 2002; 346: 557-563.

4. Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Müllner M; Collaborative Group on Induced Hypothermia for Neuroprotection After Cardiac Arrest. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Crit Care Med. 2005 ;33(2):414-8.
5. Holmgren C1, Bergfeldt L, Edvardsson N, Karlsson T, Lindqvist J, Silfverstolpe J, Svensson L, Herlitz J. Analysis of initial rhythm, witnessed status and delay to treatment among survivors of out-of-hospital cardiac arrest in Sweden. Heart. 2010 Nov;96(22):1826-30.
6. Dumas F, Grimaldi D, Zuber B, Fichet J, Charpentier J, Pène F, Vivien B, Varenne O, Carli P, Jouven X, Empana JP, Cariou A. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. Circulation. 2011 Mar 1;123 (8):877-86.
7. Sandroni C, Cavallaro F, Antonelli M. Therapeutic hypothermia: is it effective for non-VF/VT cardiac arrest? Crit Care. 2013 Mar 19;17(2): 215.
8. Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol. 2009 Apr 3;133(2):223-8
9. 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 Aug 17; 122(7):737-42.
10. Diao M, Huang F, Guan J, Zhang Z, Xiao Y, Shan Y, Lin Z, Ding L. Prehospital therapeutic hypothermia after cardiac arrest: a systematic review and meta-analysis of randomized controlled trials. Resuscitation. 2013 Aug;84(8):1021-8
11. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, Copass MK, Carlbom D, Deem S, Longstreth WT Jr, Olsufka M, Cobb LA. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA. 2014 Jan 1;311(1):45-52.
12. 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 Dec 5;369(23):2197-206.