

Therapeutic Hypothermia for Cardiac Arrest: Yes, We Can

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Physicians and researchers around the world continue to seek means to improve neurologic survival after cardiac arrest; the majority of patients who are resuscitated from cardiac arrest never awaken despite receiving high quality critical care.^{1,2} Recent data from ten communities in North America demonstrate survival to hospital discharge ranges from 3% to 39.5% for cases of ventricular fibrillation, regardless of neurologic outcome.³ Good neurologic recovery can be achieved in only 11% to 48% of resuscitated patients, the balance either die during their hospital stay or remain alive with severe neurologic deficits.^{4,5}

The neuroprotective potential of induced hypothermia had been suspected for decades based on experiments in animals and humans. The precise mechanism by which hypothermia confers protection is unknown, although many mechanisms have been proposed including slowing destructive enzymatic processes, protection of lipid membrane fluidity, and reduction in oxygen requirements. In addition, investigators have shown that hypothermia reduces lipid peroxidation, brain edema, intracellular acidosis, oxidative stress, and apoptosis of neuronal cells. Induced hypothermia was used in humans in the 1950' to protect the brain initially during cardiac surgery and subsequently after cardiac arrest. Because of hemodynamic and respiratory problems with moderate hypothermia (28°-32°C), these early protocols were abandoned. In the late 1980's, the application of mild hypothermia (32°-34°C) was shown to be beneficial in an animal model of cardiac arrest renewing interest in the use of mild hypothermia in cardiac arrest patients. Several pilot

trials of mild hypothermia in the late 1990's found improved neurologic function compared with historic controls. Two seminal studies published in 2002 demonstrated improved survival and neurologic outcome in hospitalized survivors of out-of-hospital ventricular fibrillation that received therapeutic hypothermia (TH).^{6,7} This finding prompted the International Liaison Committee on Resuscitation to recommend induced hypothermia for comatose survivors of ventricular fibrillation.^{8,9} Despite these findings, multiple barriers still exist in implementing routine use of therapeutic hypothermia after resuscitation from cardiac arrest. They include: lack of institutional policies and protocols and resources,¹⁰ perceptions of inadequate evidence,¹¹ and technical challenges.¹¹

Investigators and clinicians have used many different cooling methods, from simple ice packs, to cooling blanket, which are automated with temperature sensors, to infusion of cold fluid, to cooling catheters, which are placed into the inferior vena cava. The optimal method of cooling needs to be determined and all of these techniques vary in terms of rapidity of cooling and invasiveness.

In this issue of *Revista Española de Cardiología*, Castrejón et al¹² have demonstrated the generalizability of induced hypothermia in the Spanish critical care setting. They undertook a retrospective review of all patients treated in their intensive care unit after being resuscitated from cardiac arrest; they used a group of 41 patients who received therapeutic hypothermia as their case group. For controls, they utilized a 28 patient group that was eligible for cooling but did not receive the treatment based on a clinician's decision. These 2 groups were balanced in regards to sex, age, incidence of diabetes, and time to defibrillation. Of note, there was a non-statistically significant difference in the incidence of heart failure, in-hospital cardiac arrest, and time until initial patient care.

The authors evaluated the neurological status of their patients on discharge and after 6 months using the Glasgow cerebral performance categories.¹² The unadjusted relative risk of having good cerebral performance at 6 months was 2.16 in the hypothermia

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group (95% CI, 1.05-3.36). This was also the case at time of discharge; the unadjusted relative risk of having good cerebral performance was 2.46 in the hypothermia group (95% CI, 1.11-3.98).

The authors recognized that these results could be confounded by exposures other than therapeutic hypothermia, so they undertook adjustment for significant variables using logistic regression.¹² The effect of hypothermia treatment remained significant after adjustment for many variables. It did not reach significance when adjusted for Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, reflecting the need for a larger sample size.

The design of this study is not without limitations, which are well addressed by the authors.¹² The most important limit is the possibility of selection bias when the treating clinician chose to use hypothermia or not. It is possible that skilled critical care physicians are able to recognize and predict which patients will not benefit from cooling, leading to an increase in poor cerebral performance in the control group. It is also possible that the ICU care team subconsciously decreases the aggressiveness of care when a patient is not cooled, leading to worsened cerebral performance in the control group. They discuss this and go on to explain that the use of therapeutic hypothermia increased as providers gained experience. It is also possible that the focus on one post-resuscitative care component (hypothermia) caused other changes in the care process for survivors of cardiac arrest which could explain the difference in cerebral performance in the two groups. They had too few patients to afford further subgroup analysis.

Despite these limits associated with design, Castrejón et al¹² have successfully demonstrated that therapeutic hypothermia can be applied in the Spanish ICU setting and that neurologic outcome after cardiac arrest can be improved.

Several key questions remain regarding the universal utilization of therapeutic hypothermia. Should we be employing therapeutic hypothermia on all comatose survivors of cardiac arrest regardless of their arrest rhythm? There are little data to guide critical care providers and cardiologists in this area. Several authors have reported cooling patients in pulseless electrical activity or asystole,¹³⁻¹⁶ but there are not enough cases to perform any statistical testing.

In another study, Oddo et al compared the survival and neurologic outcome of 74 patients, all of whom they treated with TH. Compared to the survival of patients resuscitated from VF, those with asystole and pulseless electrical activity had a marked lower survival (16.7% vs 60.5%; $P<.001$). Only 8.3% of the non-VF rhythm patients had

good neurologic outcome compared to 55.3% of the VF survivors ($P<.001$).¹⁷ The survival and good outcome of the non-VF group is still better than some communities attained in a multi-community observations published by the Resuscitation Outcomes Consortium.³

Further study is needed to continue to advance our knowledge in the application of therapeutic hypothermia for comatose survivors of cardiac arrest. The next steps in these investigations need to focus on the utility of pre-hospital cooling, intra-arrest cooling and the use of hypothermia for survivors of in-patient and non-VF cardiac arrest.

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