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Therapeutic Hypothermia for Cardiac Arrest

Dr. Jean Baptiste Lascarrou, MD
******@***chu-nantes.fr

Medical Intensive Care Unit, Nantes University Hospital
Clinical Researcher - Clinical Research in Intensive Care and Sepsis (CRICS)
Member - Association des Reanimateurs du Centre Ouest (ARCO)
Previously: Medical-Surgical Intensive Care Unit, District Hospital Centre, La Roche-sur-Yon

Dr. Jean Reignier, MD
******@***chu-nantes.fr

Clinical Research in Intensive Care and Sepsis (CRICS)
Member - Association des Reanimateurs du Centre Ouest (ARCO)
Full Time Practitioner - Medical Intensive Care Unit, University Hospital Centre, Nantes

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Targeted temperature management is the key intervention for improving neurological outcomes after cardiac arrest. We discuss new data on the optimal timing and modalities of targeted temperature management.

It took nearly half a century, from 1957 to 2002, for therapeutic hypothermia to acquire its current status as a key intervention for improving neurological outcomes in survivors of cardiac arrest. Despite growing interest from healthcare workers and researchers, many questions remain unanswered regarding this treatment tool. Recent large multicentre trials raised as many questions as they provided answers. In this review, we will try to reconcile new and old data, explain discordant results, and discuss future trials of therapeutic hypothermia and other aspects of the management of cardiac arrest survivors.

Indications of Therapeutic Hypothermia

Cardiac Arrest in Shockable Rhythm

For the past 12 years, treatment decisions for cardiac arrest survivors have relied largely on two trials reported in 2002 (Hypothermia after Cardiac Arrest Study Group 2002; Bernard et al. 2002). Both trials showed improved neurological outcomes with hypothermia between 32° and 34° compared to normothermia after cardiac arrest in shockable rhythm. The vast majority of observational, retrospective, and propensity-adjusted cohort studies support this finding. The landmark Targeted Temperature Management (TTM) trial reported in 2013 (Nielsen et al. 2013) failed to demonstrate any difference in neurological outcomes or survival between hypothermia at 33° and hypothermia at 36°C. The results of the TTM trial complicate the interpretation of another preliminary study showing better outcomes with hypothermia at 32°C compared to 34°C (Lopezde-Sa et al. 2012).

These data have generated active controversy. The International Liaison Committee on Resuscitation (ILCOR) issued the following statement:

> *Pending formal consensus on the optimal temperature, we suggest that clinicians provide post-resuscitation care based on the current treatment recommendations. We accept that some clinicians may make a local decision to use a target temperature of 36°C pending this further guidance (ILCOR 2013).*

The European Resuscitation Council (ERC) new guidelines issued in October 2015 specify: “maintain a constant, target temperature between 32°C and 36°C for those patients in whom temperature control is used” (Nolan et al. 2015).

Several considerations may help to reconcile new data from trials of TTM and older results. First, TTM at 36° is not normothermia [37°]. The difference in neurological outcomes between two groups depends on the temperature difference: for instance, a 3° difference [e.g., 33° vs. 36°] may produce a 33% smaller benefit than a 4° difference [e.g., 33° vs. 37°]. Second, the control groups were not comparable between the trials reported in 2002 (Hypothermia after Cardiac Arrest Study Group 2002; Bernard et al. 2002) and 2013 (Nielsen et al. 2013). Interest in the management of cardiac arrest increased massively during this interval, leading to marked improvements in outcomes, due not only to TTM, but also to changes in the management of heart disease, notably the use of coronary angiography (Dumas et al. 2012), haemodynamics and gas exchange. The benefits from these other interventions may decrease the relative effects of TTM to levels detectable only in large sample sizes. Third, 10% to 20% of patients survived without marked neurological damage (Cerebral Performance Category 1 or 2) in subgroups with favourable prognostic factors (bystander cardiopulmonary resuscitation and short low-flow time) in the 2002 trials and in patients with poor prognostic factors (no bystander, longer low-flow time and, above all, non-shockable rhythm) in recent trials. Conceivably, patients with more severe brain damage may benefit from lower temperatures, e.g., 33°C instead of 36°C. In several retrospective studies, benefits from TTM at 33°C were more marked in patients with longer no-flow or low-flow times (Testori et al. 2012; Kagawa et al. 2010; Drennan et al. 2014), but this result was not replicated in a post hoc analysis of data from the TTM trial (Kjaergaard et al. 2015).

Cardiac Arrest in Non-Shockable Rhythm

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Patients with cardiac arrest in non-shockable rhythms now account for the majority of patients admitted to the ICU after the return of spontaneous circulation (ROSC) (Wong et al. 2014). Their prognosis is considerably poorer compared to that of patients with cardiac arrest in shockable rhythms. Nevertheless, very few data are available on this specific population, which is more heterogeneous than the population with cardiac arrest in shockable rhythm, as causes include heart disease, pulmonary embolism, asphyxia, hanging and many other conditions. Except for a subgroup analysis in the TTM trial (Frydland et al. 2015), no data from randomised trials are available. Guidelines still recommend TTM after non-shockable cardiac arrest. An ongoing trial will provide information on this growing population of cardiac arrest survivors (Lascarrou et al. 2015).

1. Modalities of Targeted Temperature management (Nau et al. 1992)

Induction of TTM

Recent data on conducting TTM, particularly the induction phase, are available. Earlier induction seemed associated with better outcomes in animal experiments and small observational studies. However, no adequately powered trial in humans has confirmed this possibility. Pre-hospital induction of mild hypothermia by infusing 4°C normal saline immediately after ROSC not only failed to improve neurological outcomes, but was also associated with higher rates of re-arrest and acute pulmonary oedema (Kim et al. 2014). However, this trial has several methodological weaknesses: only 77% of patients managed with pre-hospital hypothermia subsequently received hospital maintenance of hypothermia, and oxygenation level was unusually high in the patients diagnosed with acute pulmonary oedema. A major source of bias in studies of TTM is the faster speed of cooling in the sickest patients, due to absence of the hypothalamic response to cooling (Lin et al. 2014). There is probably a need for studies of fluids other than normal saline for inducing hypothermia. In particular, balanced crystalloid solutions (Hartman's solution and others) are generating considerable attention for managing sepsis, and may deserve similar interest in the treatment of cardiac arrest survivors. Finally, an intranasal cooling system for inducing hypothermia in the field, with no fluid infusion, is under investigation (Nordberg et al. 2013).

Maintenance of TTM

Hypothermia can be maintained using a specific internal or external device equipped with a temperature control driver or using non-specific means, such as a makeshift tent and conventional ice packs. Studies of specific devices, including a recent randomised trial (Deye et al. 2015), showed no improvement in neurological outcomes compared to nonspecific means, although nurse workload was lower.

Duration of TTM and Rewarming Phase

No adequately designed trial is available for guiding decisions about the duration of hypothermia or the speed of rewarming. Based on the trials reported in 2002, TTM is usually maintained for 12-24 hours. However, the longer duration used in the TTM Trial may have beneficial effects, notably on the inflammatory response (Bisschops et al. 2014). Another trial addressing hypothermia duration is under way [NCT02035839] (Zoll Circulation Inc 2015). Last, findings from observational studies support a slow pace of rewarming, and further information on this point will be provided by an ongoing trial [NCT02555254] (Centre Hospitalier Departemental Vendee 2015).

2. Patient Management During Therapeutic Hypothermia

A specific protocol adapted to local conditions must be developed and applied to optimise neurological outcomes after TTM (Sunde et al. 2007). All healthcare workers must adhere to guidelines (Orban et al. 2012; Camp-Rogers et al. 2013). Sedation and analgesia are necessary during TTM induction, maintenance and rewarming, but interfere with the neurological examination, thereby hindering outcome prediction. The predicted neurological prognosis is a major consideration when deciding whether treatment limitation decisions are in order. There is some evidence that drugs with short half-lives, such as propofol and remifentanil, may deserve preference over drugs with longer half-lives, such as midazolam and fentanyl (Bjelland et al. 2012). TTM is often associated with shivering. The first-line treatment of shivering is adjustment of the sedation and analgesia. If shivering persists, surface counterwarming, dexmedetomidine, or neuromuscular blockade may be used depending on the local protocol. Recent data suggest beneficial effects of neuromuscular blockade on neurological outcomes (Lascarrou et al. 2014; Salciccioli et al. 2013), but the level of evidence is low and further studies are needed.

3. Side Effects

Recent trials have improved our understanding of the risk/benefit ratio of TTM. Most adverse effects are well-known and have no effect on mortality or morbidity; examples include changes in the electrocardiogram or in serum potassium levels. A few are more serious and can lead to increased morbidity. The pathophysiological effects of hypothermia explain the increased risk of bacterial pneumonia associated with TTM in all studies. This risk is particularly high in cardiac arrest patients, whose upper airways are unprotected until endotracheal intubation is performed. Nevertheless, no effect of pneumonia on neurological outcomes was found in recent studies, regardless of their design (observational, observational with propensity-adjusted analysis) (Gagnon et al. 2015; Perbet et al. 2011).

4. Prognostication: Early and Late

Large strides have been made in neurological prognostication since the trials reported in 2002. The two main advances are the clear definition of situations warranting treatment limitation decisions in the most recent trials and the availability of validated and accurate prognostication criteria that can be used at the bedside. These tools consist of clinical tests (Glasgow motor score and brainstem reflexes), serum assays of neuron-specific enolase and S-100B, evoked potential recordings and electroencephalography and magnetic resonance imaging (MRI). Neurological prognostication now relies on a combination of findings obtained using these tools. It cannot be performed accurately until 72 hours after the arrest, except when the prognosis is catastrophic, defined in the TTM trial for instance as "the patient becomes brain dead, has an early myoclonus status or, if there are strong ethical reasons to withdraw intensive care" (Nielsen et al. 2013). Recent European guidelines (see Figure 1) provide clinicians with useful guidance (Sandroni et al. 2014). However, according to a recent survey intensivists vary widely regarding the tools they use for neurological prognostication, and their decisions may be based as much on beliefs as on science (Friberg et al. 2015).

Predicting a poor neurological prognosis is important to determine whether life-sustaining interventions should be withheld or withdrawn. There is growing evidence that factors predicting a good prognosis can be assessed during TTM. Thus shivering (Nair and Lundbye 2013) and bradycardia (Staer-Jensen et al. 2014; Thomsen et al. 2015) during TTM are associated with better outcomes. Furthermore, although the use of specific cooling devices does not affect patient outcomes, they indicate how much power is needed to cool the patient, and greater power is associated with better outcomes (Murnin et al. 2014).

Predictors of neurological outcomes must be well characterised both for designing trials of individualised treatment strategies and to provide accurate information to the family. Attention to cognitive impairments and emotional difficulties in cardiac arrest survivors may improve outcomes even in the medium and long term (Moulaert et al. 2015).

Conclusion

Although recent efforts have chiefly targeted the first three links in the chain of survival (Becker et al. 2015), we must keep in mind that TTM is the only intervention proven to favourably affect the fourth link. Huge knowledge gaps still exist regarding all aspects of patient management during TTM. Further trials are needed to fill these gaps and to provide the information needed to develop individualised treatment strategies.

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See Also: Therapeutic Hypothermia in Severe Trauma

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