Induced Hypothermia for Neuroprotection: Understanding the Underlying Mechanisms

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Introduction

In the past few years, the use of therapeutic hypothermia as a tool to mitigate neurological injury has gained a firm foothold in many intensive care units (ICU) throughout Europe and, to a lesser degree, in the United States. Currently, in the adult setting its most widespread use is in patients who remain comatose after cardiac arrest. Several studies using historical controls, followed by two randomized controlled trials, have demonstrated that use of induced hypothermia following cardiac arrest improves neurological outcome in patients with witnessed arrests and an initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) [1, 2]. These benefits were observed in spite of the fact that the speed of induction of hypothermia (cooling rates) was relatively slow, especially in the larger of the two studies; target temperatures were achieved only after an average period of 8 hours in the multicentered Hypothermia after Cardiac Arrest (HACA) trial [1]. In the second study, where cooling was initiated very early (in the ambulance during the patients’ transport to the hospital, by administering refrigerated fluids), cooling rates were much faster, although it still took about 2½ hours to reach target temperature [2]. Regarding the observed benefits, the HACA trial reported an absolute increase in rates of favorable neurological outcome of 16% (relative increase 41%); an absolute increase of 23% (relative increase 88%) was reported in the second study. A meta-analysis by Holzer et al. [3] concluded that the number needed to treat to achieve one additional patient with a good neurological outcome was 6, a number that compares very favorably to many other interventions both inside and outside of the ICU setting. Preliminary evidence suggests that there may be benefits in patients with witnessed cardiac arrest regardless of the initial rhythm [4]. Based on the results of these studies the International Liaison Committee on Resuscitation issued a recommendation that hypothermia be used in patients following witnessed out-of-hospital cardiac arrest if the initial rhythm was VT or VF, and to consider its use for other rhythms and for in-hospital cardiac arrest [5].

Favorable effects of hypothermia in mitigating post-anoxic cerebral injury have also been observed in a number of non-randomized and in two multicentered randomized studies in newborns with perinatal asphyxia. In the two RCTs, hypothermia was initiated 5 to 6 hours after birth and applied for a period of 72 hours; significant improvements in the rates of favorable neurological outcome were observed, with the greatest benefits being observed in patients with less severe injuries [6, 7].

In a separate but closely related issue, it is becoming clearer that the development of fever in patients with neurological injury is an independent predictor of
adverse outcome, and that fever may cause significant additional neurological injuries in these patients. Thus, maintaining normothermia may help mitigate or prevent some of these injuries [8, 9].

In contrast to these positive findings, studies in patients with traumatic brain injury have produced conflicting results [9, 10], and studies looking at short-term induction of hypothermia in the peri-operative setting have been negative [11]. These negative findings in some studies have led to heated debates on the role of hypothermia in general, and have hindered the introduction of hypothermia even in those cases where the evidence is strong.

### Historical Perspective

To understand better the reasons for the negative results of some studies and the positive results of others, we should look firstly at the physiological aspects and at the processes that we are trying to influence when we use therapeutic hypothermia. A better understanding of the mechanisms underlying brain injury and hypothermia’s potential protective effects will help us to properly use hypothermic treatment and avoid the (potentially severe) side effects of hypothermia. A lack of such understanding has almost certainly contributed to the failure of some of the hypothermia trials to date. This is illustrated by some of the early experiences with induced hypothermia in the 1950s and 1960s, when it was used in the treatment of cardiac arrest and traumatic brain injury and in the perioperative setting during cardiac surgical and neurosurgical procedures. At that time it was thought that hypothermia exerted its effects exclusively by reducing brain metabolism, with concomitant decreases in oxygen and glucose demand. Based on this assumption of the underlying mechanism, patients were mostly treated with deep hypothermia (≤30°C). The core temperatures that were actually achieved varied considerably both between different patients and within the same patient, because the available cooling and rewarming methods were not very reliable and the patients’ temperatures could, therefore, not be easily controlled. The most frequently used cooling methods were placement of slabs of ice, ice pads and refrigerated water on the patient’s skin. Because no intensive care facilities were available, the treatment was applied in general wards. Duration of cooling also varied considerably.

In spite of this lack of precise and well-controllable cooling methods and the use of temperatures below 30°C (which is associated with a much greater risk of severe side effects compared to temperatures ≥30°C [8, 9]), some of these studies appeared to show benefits compared to ‘expected outcome’ or historical controls. However, the reported benefits were variable and uncertain; in addition, there were significant problems in patient management and severe side effects. These problems led to the discontinuation of prolonged hypothermia as a medical treatment following cardiac arrest, traumatic brain injury and most other indications at that time, although hypothermia continued to be used in the peri-operative setting. These experiences graphically illustrate the difficulties involved in trying to improve patient outcome with induced hypothermia.

However, interest in hypothermia treatment was rekindled in the early 1980s by the positive results of a large number of animal experiments in various types of brain injury. Hypothermia was found to be effective in models for global ischemia, focal ischemia, traumatic brain injury and ischemic or hemorrhagic stroke. Many important insights regarding the most effective use of hypothermia, as well as more