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Induced Hypothermia as a Neuroprotectant in Post-Cardiac Arrest

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ABSTRACT

Survivors of out-of-hospital cardiac arrest frequently suffer devastating effects from anoxic brain injury. Therapeutic hypothermia is the first therapy to show benefit in improving survival as well as limiting neurologic injury. We review the data supporting the use of therapeutic hypothermia in this patient population, the pathophysiologic basis of its neuroprotectant effects, the methods of hypothermic induction, and the clinical application.

HISTORICAL ASPECT

Hypothermia as a therapy for the prevention of anoxic brain injury after cardiac arrest was introduced in the early 1950s by Benson and colleagues.[1] Their initial trial included 19 subjects and investigated the benefits of induced hypothermia (IH) for neuroprotection in patients who had suffered cardiac arrest. Twelve patients received hypothermia, and 7 patients received conventional therapy. The author reported a 58% survival rate (7 patients) in the hypothermia group compared to a 14% survival rate (1 patient) in the normothermia group. Favorable neurological outcomes (no major neurological deficits) were documented in 100% of the surviving patients in the hypothermic group.

Decades later, after numerous therapeutic modalities had fallen short in preventing anoxic brain injury,[2,3] interest in hypothermia was revived. In the late 1990s, six preliminary studies[4–9] evaluating the feasibility and safety of IH in post-cardiac arrest (PCA) patients showed positive results. Then, in 2002, the results of two major randomized controlled trials in Europe[10] and Australia[11] became available. In the European study[10] (Hypothermia After Cardiac Arrest study group), 275 patients successfully resuscitated from cardiac arrest were randomized to hypothermia or normothermia. Seventy-five of the 136 patients in the hypothermia group (55%) had a favorable neurologic outcome as compared with 54 of 137 (39%) in the normothermia group. Mortality at 6 months was 41% in the hypothermia group and 55% in the normothermia group. In the Australian study,[11] 77 PCA patients were randomized in similar fashion. Twenty-one of the 43 patients treated with hypothermia (49%) survived to hospital discharge as compared with 9 of the 34 treated with normothermia (26%). Results from these studies were revolutionary and represented a pivotal point in the management of PCA patients to improve both neurological outcome and survival. These publications prompted the International Liaison Committee on Resuscitation[12] (ILCOR) to publish an advisory statement in 2003 recommending the application of IH in the United States for survivors of out-of-hospital arrest whose initial rhythm is ventricular fibrillation (VF) or ventricular tachycardia (VT). Since that time, many national and international medical societies, including the American Heart Association,[13] have updated their guidelines to include IH in the treatment of patients with out-of-hospital cardiac arrest.

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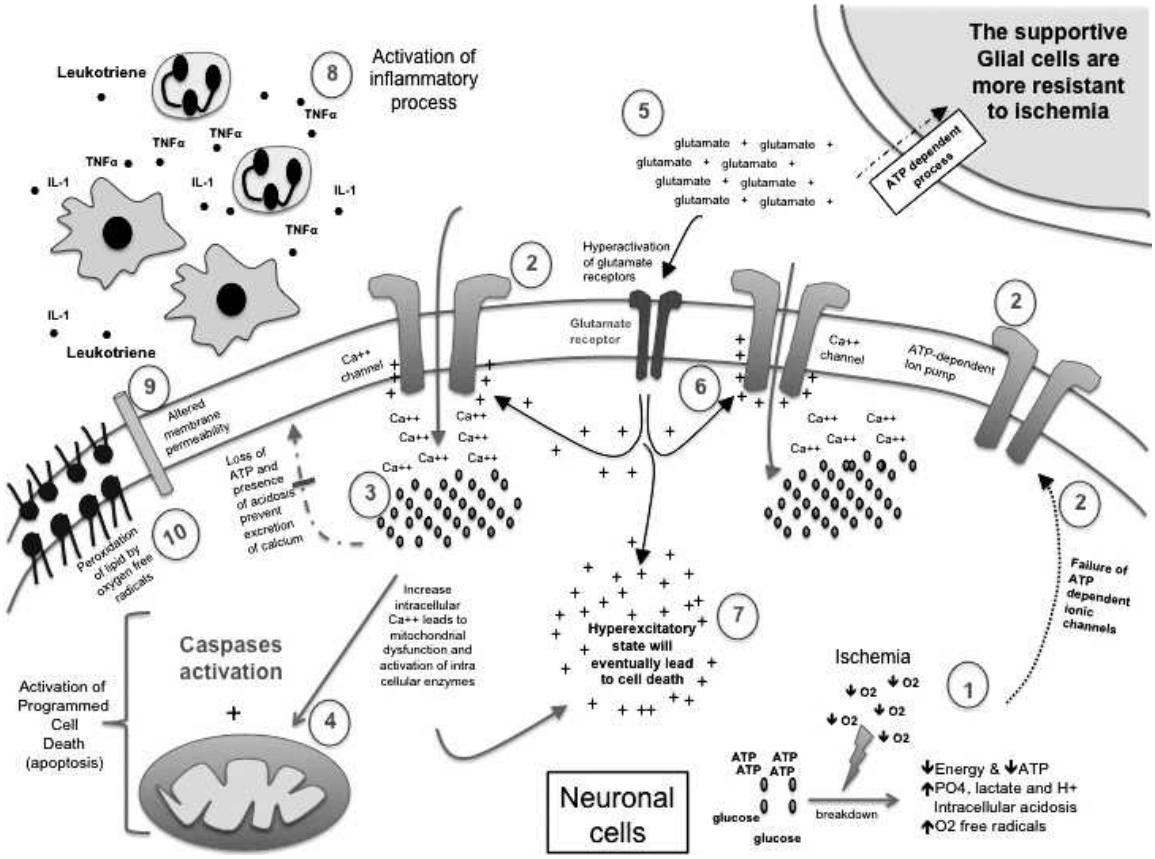
MECHANISM OF NEUROPROTECTION WITH IH

The mechanism of neuronal injury in the cardiac arrest patient is a result of two successive events: ischemic injury from hypoxia and the reperfusion-related injury that follows restoration of blood flow. Immediately after the arrest, blood supply to the brain is minimal, and the brain becomes depleted of oxygen within 20 seconds.[14] This is followed by the consumption of adenosine triphosphate (ATP) and glucose stores within 5 minutes.[15,16] Anaerobic glycolysis and lipolysis take place, inorganic acids and fatty acids accumulate, and intra- and extracellular acidosis develops. Finally, cell membrane ATP-dependent ion pumps fail, leading to the buildup of intracellular calcium and extracellular glutamate.[17,18] This sequence of events leads to a state of cellular hyperex-



Mechanisms of brain injury in post-cardiac arrest patients. 1. Ischemia causes cerebral oxygen and glucose consumption and decreases in available ATP, which will end up activating anaerobic glycolysis and the production of inorganic acids and acidosis. 2. ATP-dependent ionic channels will fail, causing disturbance in cellular homeostasis. 3. Ca++ will accumulate inside the cells secondary to the lack of available ATP and acidosis. 4. Intracellular Ca++ will lead to mitochondrial dysfunction, activation of lytic enzymes, and induction of immediate early genes. 5. Glutamate will accumulate secondary to decreases in the energy-dependent reuptake process. 6. Excess glutamate will lead to persistent activation of glutamate receptors, which in turn will further activate Ca++ receptors and induce more Ca++ entry. 7. A state of neuronal hyperexcitability (excitotoxic pathway) is created, which promotes injury and necrosis. 8. Ischemia will also activate an inflammatory process, causing the release of many toxic mediators (TNF-α, IL-1) and the attraction of inflammatory cells that extend the risk of cell damage. 9. Impaired membrane permeability secondary to ischemia will impair fluid balance. 10. Lipid peroxidation by oxygen-free radicals causes more membrane damage.

citability terminating in diffuse cellular damage and necrosis. If resuscitation is successful and blood flow is restored, rapid metabolism of accumulating arachidonic acid leads to free radical formation, peroxidation of phospholipids, and further membrane damage. Cellular death during this phase is believed to be due to apoptosis (programmed cell death), governed by calcium-related mitochondrial injury[19] and activation of caspases, which degrade intracellular proteins (Figure).[20–22]

Hypothermia affords protection against both phases of cellular injury. The putative mechanisms of its benefits are myriad and remain incompletely elucidated, but its potency appears related to a blanket effect on numerous metabolic pathways. The cerebral metabolic rate decreases 6%–7% with each 1°C drop of temperature,[16,23] which in turn improves relative oxygen supply to the brain and slows adverse temperature-dependent cellular reactions.[24] Hypothermia also inhibits the excitotoxic state, prevents mitochondrial dysfunction,[19] and diminishes caspase activation.[20–22] It decreases free radical formation[25,26] and inhibits the inflammatory response related to ischemia.[27–31]

CLINICAL APPLICATION

Therapeutic hypothermia in the treatment of PCA patients is rapidly taking root, but the frequency of its application in the United States is still quite limited. An internet-based physician survey in 2006 found that 74% of responding physicians, most of whom were attending physicians at teaching hospitals, had never

used therapeutic hypothermia. Adoption among intensivists was 34%, while only 16% of emergency medicine physicians reported use.[32] Reasons for under-application include a perceived paucity of data and difficulty in the technical implementation of hypothermic therapy.

Existing modes for induction vary from rudimentary methods such as fanned cold air, ice packs, and cooling blankets to the more invasive: ice-water bladder lavage, gastric lavage, and rapid ice-cold IV fluid infusion. More complex methods include the use of a cooling helmet,[33] an extracorporeal heat exchanger (animal study in 2001),[34] and endovascular cooling catheters.[35] The Arctic Sun cooling blanket (Medivance, Louisville, CO)[36] and the ThermoSuit (Life Recovery Systems, Waldwick, NJ)[37] are recently introduced devices that rely on skin-applied adhesive pads and a circulating cold-water bath, respectively.

Hypothermic induction can begin immediately upon successful resuscitation and return of spontaneous circulation. If emergency medicine responders are trained to do so, cooling can begin in the prehospital setting.[11] Otherwise, cooling is instituted as soon as possible in the emergency department in concert with necessary measures for hemodynamic stabilization. Coronary angiography with potential percutaneous coronary intervention is frequently performed early in the course of management, as acute coronary syndrome is a common precipitating factor in cardiac arrest.[38,39] Management of thermoregulation (32°C to 34°C for 12–24 hours followed by gradual rewarming at a rate of 0.3°C to 0.5°C per hour) occurs in the intensive care setting where mechanical ventilation and careful hemodynamic and laboratory monitoring are possible. Sedation and anesthesia are provided as necessary, and if shivering persists despite these measures, paralytic agents may be used to suppress heat generation.

FUTURE OF IH IN PCA NEUROPROTECTION

Hypothermia is currently the only neuroprotectant with proven benefits in the prevention of PCA anoxic brain injury and is currently recommended for out-of-hospital cardiac arrest victims with VF or VT as the initial rhythm. Guidelines also recommend consideration of hypothermia for other types of cardiac arrest,[13] and recommendations for hypothermia for in-hospital cardiac arrest are likely to follow soon. Recent advances in the science include more sophisticated cooling devices, which improve induction rates and facilitate tight thermoregulation within the therapeutic temperature zone. Current areas of investigation for hypothermic therapy include ST-segment elevation myocardial infarction and stroke, both of which are present in epidemic proportion in the United States and which share a therapeutic goal of limiting necrosis in ischemic tissue. As further data surface from future clinical trials, evidence for broader application of hypothermia for a variety of disease entities is likely.

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