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EDITORIAL

Cerebral Edema After Cardiac Arrest: Tell Tale Sign of Catastrophic Injury or a Treatable Complication?

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Despite advances in cardiopulmonary resuscitation (CPR) for cardiac arrest being proposed as early as the 1950s [1] and 1960s [2], only in the modern era has the use of specific interventions such as post-arrest therapeutic hypothermia [3] and community-wide emergency medical services, like bystander-initiated CPR and first responder defibrillation [4], consistently demonstrated a benefit to survival. In addition, a recent Cochrane review has determined that the only strategy that has shown improvement in neurologic outcome after cardiac arrest is induction of mild therapeutic hypothermia [5].

Diffuse brain edema early after cardiac arrest is often associated with a dismal neurological examination and poor outcomes, and the use of osmotic agents has not been shown to reverse or improve either. Clear guidance on how to manage cerebral edema post-cardiac arrest has not been established, and efforts in this regard may possibly be futile.

Intensivists from prior generations presciently anticipated a need for brain-oriented resuscitative measures and therapies [6]. However, the pathophysiologic mechanisms of cardiac arrest associated with secondary inflammatory and hormonal responses, during and after resuscitation [also known as post-cardiac arrest syndrome (PACS)] [7], and with secondary brain injury like cerebral edema formation have only recently been established from a molecular biologic basis. More recently, water transport channels, such as Aquaporin-4 (AQP4) [8] and Sur1-Trmp4 [9], are now being evaluated as potential secondary targets for inhibiting cerebral edema formation after cardiac arrest.

The mechanisms of cardiac arrest-induced cerebral edema formation are likely multifactorial; however, one main mechanism thought to be related is the perivascular pool of AQP4, which is rate limiting for water influx during cerebral edema formation and the site of action for osmotic agents that cause brain water efflux [10]. Although it has been known for two decades that the perivascular pool of AQP4 localizes to the astrocyte endfeet adjacent to the blood–brain barrier, progress in the identification of small-molecule aquaporin inhibitors has been exceedingly slow [11].

In this issue of Neurocritical Care, Nakayama et al. [10] report their results on attenuating cerebral edema and blood–brain barrier disruption after successful resuscitation from an 8-min arrest induced with intravenous potassium chloride in a mouse model. In their series of well-designed experiments, they found that a continuous intravenous infusion of conivaptan, a V1a and V2 antagonist, targeting a serum osmolality goal of approximately 350 mOsm/L, attenuates regional brain edema development, particularly in the caudo-putamen complex and cortex via the perivascular AQP4 pool (areas where the perivascular pool of AQP4 is more prevalent). The novel use of intravenous conivaptan, a dual arginine vasopressin (AVP) receptor antagonist, is thought to be mediated through its antagonism on V1a receptors in the brain via interactions with AQP4, and on V2 receptors by downregulating AQP2 channel expression in the kidney, which can induce diuresis. The efficacy of water efflux requires maintaining a

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hyperosmolar state of ~350 mOsm/L, which was achieved by the higher dose of conivaptan (0.3 mg/kg/day). In one of the subsequent arms of the experiment, conivaptan also was found to decrease the amount of blood–brain barrier disruption 48 h after cardiac arrest and resuscitation.

The experiments were conducted in a thoughtful and elegant manner. In addition to the use of wild-type mice, the authors also had a comparison group of targeted disruption of the gene encoding α-syntrophin (α-syn), which have a diminished perivascular AQP4 pool. Additionally, conivaptan was studied at two different doses, and only the higher dose (0.3 mg/kg) showed an effect on water content compared with controls. The animals who were α-syn negative demonstrated no response to conivaptan, lending further credence to the role of AQP4 in cerebral edema formation, as well as the effectiveness of conivaptan in decreasing this edema.

The authors readily recognize the limitations of their study, including the fact that the flow of water across the blood–brain barrier is not exclusively mediated by aquaporin-4, and there may be other agents to study and mechanisms to target. Of note, some other agents have shown similar promise, such as glibenclamide, which acts at the sulfonylurea receptor 1 (SUR1) in combination with transient receptor potential M4 (TRPM4). The SUR1-TRPM4 complex is implicated in cerebral edema formation in multiple disease states, and its blockade with glibenclamide has been shown to ameliorate brain edema without causing significant hypoglycemia (glibenclamide is a sulfonylurea, similar to glyburide, which is used in humans). [9] Recent clinical trials in humans of glyburide in malignant cerebral infarction have shown great promise, and will likely be the focus of future phase 3 studies. Cardiac arrest is a disease entity that would greatly benefit from study of these agents in humans as well.

This work by Nakayama et al. provides the first evidence to demonstrate the use of an AVP receptor antagonist to ameliorate the effects of cerebral edema caused by cardiac arrest. Next steps could include studying the agent, as well as its mechanisms, in a larger animal model, in which the hydration status of the animal could be better monitored and maintained, crucial with the use of such an agent which can cause significant diuresis. Furthermore, the time window for effectiveness needs to be better explored, as providing agents in the hyperacute period after cardiac arrest in humans will likely be tremendously challenging. Finally, the combined use of anti-edema agents with targeted temperature management would be valuable to study in the future.

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