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Opinion

Cardiorespiratory Arrest, The Unmet Challenge

Sylvia Frisancho-Kiss*

Department of Anesthesiology and Intensive Care, Hospital Komárno, Slovakia

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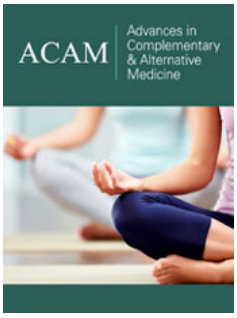

***Corresponding author:** Sylvia Frisancho-Kiss, Department of Anesthesiology and Intensive Care, Hospital Komárno, Slovakia

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Abbreviations: ACA: Acute Cardiorespiratory Arrest; CPR: Cardiopulmonary Resuscitation; ROSC: A Return Of Spontaneous Circulation; ATP: Adenosine Triphosphate; SIRS: Systemic Inflammatory Response; TLR: Toll-Like Receptor; TBI: Traumatic Brain Injury; TNFα: Tumor Necrosis Factor-Alpha; MC KO: Mast Cell Knock Out; PAR2/NF-kB: Protease-Activated Receptor-2/Nuclear Factor Kappa B

Opinion

Acute cardiorespiratory arrest (ACA) is one of the most extreme abrupt cataclysms in medicine. While intensive care possesses a bountiful chemical and technical toolbox to manage insufficient circulation and respiration, the complete cessation of these vital functions remains an unresolved predicament. Even when the arrest occurs in a previously relatively uncompromised organism in a bystander or hospital environment, and upon the realization of the dreadful peril an immediate intense professional response emerges, the overall survival rate with good life quality is low. According to USA estimates, out-of-hospital cardiac arrest managed by emergency medical services has a discharge from hospital frequency of around 11%, and in-hospital cardiac arrest has a discharge ratio of around 25%. Concerning life quality, 18 to 40% of discharged patients demonstrate moderate to severe functional impairment, while the majority of them report some degree of dysfunctionality [1]. Based on current knowledge, well-written algorithms are trained at several professional levels [2]. The mechanical support is combined with electrical levering and well-established medications circulate in the predetermined time and dose intervals to re-establish effective circulation and tissue oxygenation. An analytic approach is taken and causative therapy is introduced as well. The time window from anoxia to organ damage is variably short, supremely for the brain, receiving a luxurious 20% of cardiac output. Within 30 seconds of cerebral anoxia, isoelectric encephalography, representing cessation of brain function breaks through [3]. The permanent loss of conscience or qualitative defect in brain function represents the most debilitating determining outcomes of cardiorespiratory revival.

It is therefore perturbing to realize our limited options to preserve vital organs, in particular the brain, despite the existence of more than 83700 research publications by searching Pubmed on the subject of cardiac arrest. The trigger for cardiac arrest may be assorted and complex, but it is always accompanied by overall ischemia later reperfusion, a systemic inflammatory response, energy deprivation, collapse of voltage channels, and cell death [4]. Each predicament is abundantly dissected in basic research, yet the clinical reverberation is sparse.

Perhaps the task is cumbersome, the pathology is immense, priorities are skewed, or maybe the coordination of the effort is bereft? While knockout animals serve at addressing the constitutive function of inflammatory, ischemia, or cell death pathways, short-lived, transient postexposure modification, reflective of a conceivable change in outcome has not been addressed sufficiently in animal models or clinical trials. The recent pandemic well reflected the often hasty application of alternative approaches by professionals not trained in

translational immunology, because such a bridge hasn't been built yet, and the need hasn't been envisioned.

The priority during cardiopulmonary resuscitation (CPR) and upon return of spontaneous circulation (ROSC) is safeguarding the brain. Shortly after the cessation of oxygen delivery aerobic adenosine triphosphate (ATP) production halts, systemic inflammatory response (SIRS) with cytokine release, reactive oxygen species, and glutamate production, membrane disintegration, and swelling, discordant electrical activity, and collapse of vascular autoregulatory mechanisms emerge, culminating in cell death.

Several pro-inflammatory pathways have been addressed successfully in experimental cerebral hypoxia models. A stereotyped fear of influencing pro-inflammatory mediators is the rhetoric of "suppressing immunity ", which is conservatively viewed as uniquely designed to combat pathogens and clear debris. The proinflammatory receptor and signaling niché is complex with abundant cross-talks and targeted regimentation in an adequate time and degree has the potential to mitigate SIRS and ischemia-reperfusion with minimal effect on antimicrobial response. Demonstration of modulations tested in research settings with the potential of clinical applicability would require writing a book, but highlighting certain potential key molecules serves the purpose of viewpoint.

Traumatic and hypoxic brain injury, ischemia, hemorrhage, and neuroinflammation lead to the upregulation of TLR2 and TLR4 pattern recognition receptor-induced proinflammatory signaling pathways via endogenous ligand mechanisms [5]. Circulating monocytes of ACA patients at 12, 24, and 48 hours after insult upregulated TLR2 and TLR4 expression, with the maximum at 12 hours, emphasizing the need for genuine timing. Later monocytes became hyporesponsive to ex vivo TLR ligand stimulation, and 30-day mortality was accompanied by an immune-suppressed state. It appears, therefore, that an overreactive response later concludes in hyporesponsiveness and exhaustion [6]. Experimentally, TLR4 mutant mice had improved survival after cardiopulmonary arrest in potassium-induced ACA, with a 33% mortality over 53% in wild-type animals at day three with a similarly decreased number of apoptotic cells in TLR4 deficient animals [7]. TLR4 inhibition protects against neuronal death in mice by reducing oxidative stress in the focal ischemia model [8]. Experimental TLR4 inhibitor TAK-242 introduced 30 minutes after anoxic injury in newborn rats led to the inhibition of cerebral edema, infarct size, and improved neurobehavioral functions [9]. Clinical trials have shown no significant effect of TLR4 suppression during acute bacterial sepsis, offering a therapeutical advantage in indications of SIRS, and ischemia-reperfusion injury modification.

Complement cascade activation is an essential component of post anoxic cerebral injury. C5a anaphylatoxin is viewed to have a contributory role in ischemia models of the brain, kidney, heart, and C5a blockade was protective in numerous studies. C5a receptor inhibition just before experimental murine ischemic stroke induction demonstrated significantly decreased infarct volume, neutrophil influx, and injury size [10] similar to a traumatic brain cryoinjury (TBI) model [11] and in an oxygen-deprived neuronal environment [12]. While proximal complement block appears to have an even more pronounced effect, it may lead inadvertently to impaired microbial clearance particularly of encapsulated organisms, while targeting C5a leads primarily to decreased vascular permeability, regulated neutrophil influx, and curtailed mast cell activation.

Brain swelling (vasogenic and cytotoxic) emerging upon anoxic brain injury generates mechanical compressive damage to neurons and support structures inside the rigid skull. The molecular mechanisms of swelling are assorted. Mast cells have been shown to participate as first sentinels, immediate mediators responsive to chemical and mechanical challenges by widespread degranulation, and mediator release [13]. Cerebral swelling, induced by transient middle cerebral occlusion was successfully dampened in mast cell-deficient (MC KO) mice and animals treated with MC stabilizing agent cromoglycate. Acute drug-induced sudden death causalities resemble anaphylaxis with cardiac mast cell recruitment, degranulation, tryptase, and preformed TNFα release, contributing to myonecrosis. Among stimuli complement C5a, reactive oxygen species (ROS) and adenosine were identified [14]. Anoxic brain injury during asphyxia-induced cardiac arrest in rats impelled a massive mast cell tryptase efflux and microglial activation via PAR-2 /NF-kB pathway and proinflammatory cytokine production. In an anoxic cardiac arrest experiment on rats, animals were treated with intranasal mast cell tryptase inhibitor one hour after initial and successful CPR with mechanical ventilation, chest compression, epinephrine, and bicarbonate with ROSC within five minutes, and significantly improved short and long-term neurological outcomes were observed [15].

Cardiopulmonary arrest is a great task in the crusade to save human lives from the extreme depths of disturbance and for the pressingly short time to initiate effective action. The etiology of cardiac arrest, the time window between the event and ROSC, and the baseline condition of patients place intrinsic limits on revival efforts. Managing the patient in a peri-, and post-resuscitation situation requires fast and effective professional contrivance available in every healthcare setting. This opinion article points out that further mitigation of ACA-related brain damage presently is possible using immune modulators, at least on an experimental level.

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