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Neuroprotective strategies and neuroprognostication after cardiac arrest

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Neurocognitive disturbances are common among survivors of cardiac arrest (CA). Although initial management of CA, including bystander cardiopulmonary resuscitation, optimal chest compression, and early defibrillation, has been implemented continuously over the last years, few therapeutic interventions are available to minimize or attenuate the extent of brain injury occurring after the return of spontaneous circulation. In this review, we discuss several promising drugs that could provide some potential benefits for neurological recovery after CA. Most of these drugs have been investigated exclusively in experimental CA models and only limited clinical data are available. Further research, which also considers combined neuroprotective strategies that target multiple pathways involved in the pathophysiology of postanoxic brain injury, is certainly needed to demonstrate the effectiveness of these interventions in this setting. Moreover, the evaluation of neurological prognosis of comatose patients after CA remains an important challenge that requires the accurate use of several tools. As most patients with CA are currently treated with targeted temperature management (TTM), combined with sedative drug therapy, especially during the hypothermic phase, the reliability of neurological examination in evaluating these patients is delayed to 72–96 h after admission. Thus, additional tests,

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including electrophysiological examinations, brain imaging and biomarkers, have been largely implemented to evaluate earlier the extent of brain damage in these patients.

Introduction

Cardiac arrest (CA) is a common event, affecting >350,000 individuals in the United States and 275,000 in Europe every year [1,2]. Despite improvements in short- and long-term survival rates and neurological outcomes over the recent years [3,4], sudden CA remains an important cause of morbidity and mortality, representing the third leading cause of death in the United States [5].

The overall outcome has largely improved over the years due to better emergency care, including early and correctly administered cardiopulmonary resuscitation (CPR), bystander CPR, early defibrillation for shockable rhythms, and wider implementation of post-resuscitation care bundles [6,7]. Nevertheless, persistent postanoxic coma remains the leading cause of death among those who survived CA [8]. In particular, the occurrence of hypoxic–ischemic encephalopathy (HIE) after CA was recently integrated in the so-called "post-resuscitation syndrome", which is characterized by post-anoxic brain injury, cardiovascular impairment, and a systemic inflammatory response following the ischemia/reperfusion process [9], potentially contributing to enhanced HIE.

Clinicians must consider two important issues when managing a patient with HIE. First, the pathogenesis of HIE is complex and multifactorial (Fig. 1), making it unlikely that one therapy alone will effectively prevent or "cure" this complication. Different interventions have been evaluated in experimental models and clinical trials in this setting, although the results have been disappointing or difficult to interpret. Second, the assessment of neurological recovery in such patients is challenging, and a reliable and early method for predicting the outcome in those who remain comatose is warranted.

Thus, the aim of this review is to describe the therapies that can potentially attenuate brain injury and promote neurological recovery in comatose survivors of CA, in particular different promising drugs that are currently undergoing early clinical testing. In addition, we discuss how multimodal neurological monitoring should be used to assess the prognosis in this patient population.

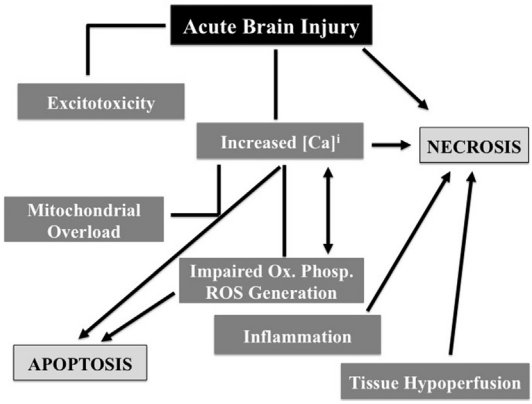

Fig. 1. A schematic summary of the main mechanisms implicated in postanoxic brain injury. Ox. Phosp. = oxidative phosphorylation; $[Ca]^i$ = intracellular calcium concentrations.