

The Brain after Cardiac Arrest

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Abstract

Cardiac arrest is common and deadly. Most patients who are treated in the hospital after achieving return of spontaneous circulation still go on to die from the sequelae of anoxic brain injury. In this review, the authors provide an overview of the mechanisms and consequences of postarrest brain injury. Special attention is paid to potentially modifiable mechanisms of secondary brain injury including seizures, hyperpyrexia, cerebral hypoxia and hypoperfusion, oxidative injury, and the development of cerebral edema. Finally, the authors discuss the outcomes of cardiac arrest survivors with a focus on commonly observed patterns of injury as well as the scales used to measure patient outcome and their limitations.

Keywords

- ▶ cardiac arrest
- ▶ brain injury
- ▶ outcomes

Cardiac arrest (CA) is the most common cause of death in the developed world, claiming over 17 million lives annually.^{1–3} Despite advances in care, the majority of patients who are treated after the return of spontaneous circulation (ROSC) will succumb to the sequelae of hypoxic-ischemic brain injury before hospital discharge. Similar to traumatic brain injury, hypoxic-ischemic brain injury after CA results in both primary and secondary injuries, with distinct mechanisms and treatment strategies (→**Fig. 1**). High-quality cardiopulmonary resuscitation (CPR) initiated as soon as possible after collapse, and early defibrillation to rapidly restore normal perfusion, are the most important interventions to reduce the severity of primary brain injury.⁴ It remains unclear whether care provided after ROSC can reduce the severity of primary brain injury or if therapies after CPR improve outcomes only by reducing the risk of secondary brain injury. Evidence-based therapies in the hours to days after ROSC that improve neurologic outcomes include targeted temperature management; early coronary revascularization; delayed, multimodal neurologic prognostication; and postacute care rehabilitation.⁵ In this review, we provide an overview of the mechanisms and consequences of postarrest brain injury as an introduction to the many specific therapies that are reviewed in depth elsewhere in this issue.

Neuronal Death after Cardiac Arrest

The physiological and molecular events associated with brain injury after CA are complex and have been described in detail.^{6–8} In the clinical setting, hypoxic-ischemic brain injury cannot be ascribed to any single mechanism. It is perhaps unsurprising then that well-controlled experiments which block or promote a single molecular pathway are ineffective for improving brain recovery,^{9,10} but pleiotropic, relatively nonspecific interventions may improve recovery. Examples of the latter include reduction of brain temperature and general anesthesia.^{11,12} Substantial current research focuses on understanding the fact that histological signs of post-CA neuronal death are delayed for hours or days after ischemia-reperfusion. This observation has prompted an analogy to other types of delayed, programmed cell death such as apoptosis, autophagy, necroptosis, and ferroptosis.^{6,13,14} No pure model of cell death is exactly like the delayed neuronal death observed after global ischemia-reperfusion, and it is probably best to consider each of these mechanisms as a potential contributor to post-CA brain injury. In patients, other macroscopic disturbances of multiple organ systems, endothelial function, and homeostatic processes also contribute to the progression of brain injury and neuronal death.

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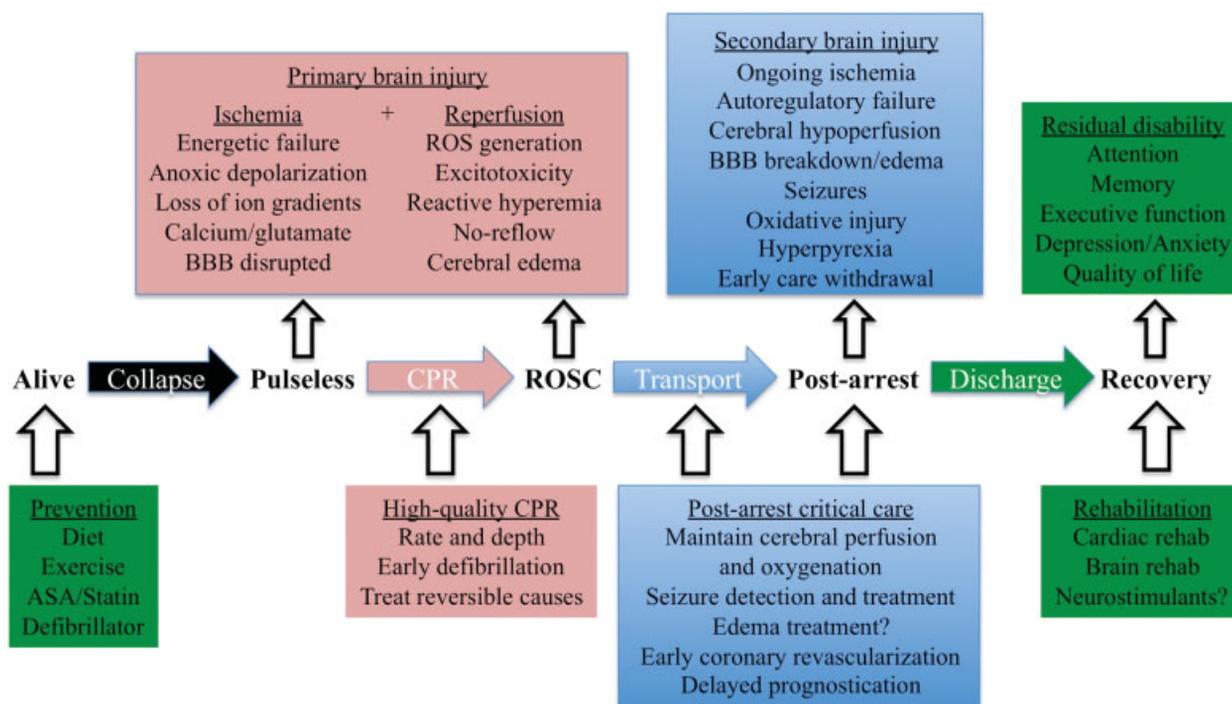


Fig. 1 Conceptual map of brain injury after cardiac arrest. ASA, aspirin; BBB, blood–brain barrier; ROS, reactive oxygen species.

Cerebral Homeostasis after Cardiac Arrest

Potentially modifiable mechanisms of secondary brain injury include seizures, hyperpyrexia, cerebral hypoxia, oxidative stress, the development of cerebral edema, microcirculatory dysfunction, impaired autoregulation of cerebral blood flow, and increased cerebral vascular resistance.^{15–24} Not all of these phenomena occur to the same degree in every patient. However, like the molecular events, each one has the potential to add to brain injury. The provision of high-quality postarrest critical care can minimize the risk from these potentially modifiable factors.

Seizures occur in 10 to 20% of comatose patients after CA, may worsen excitotoxicity, and are associated with worse outcomes.^{23,25} It remains unknown whether seizures are simply an epiphenomenon of more severe injury or by themselves produce secondary injury.^{23,24} Regardless, monitoring of the electrical state of the brain provides both prognostic information as well as guidance for intensive care treatment.²⁶

Cerebral autoregulation of blood flow can be absent or right-shifted after cardiac arrest.¹⁹ Thus, the brain is particularly sensitive to hypotension and may require higher than normal arterial pressure to maintain normal blood flow. Combined with the fact that systemic hypotension and shock after CA are also common,²⁷ and microvascular dysfunction can lead to areas of no-reflow despite return of a perfusing rhythm,²⁸ significant cerebral hypoperfusion is a real risk. Aggressive early resuscitation, coronary revascularization, and vasopressor use to increase mean arterial pressure may reduce this risk. At a population level, higher arterial pressures after CA are associated with improved patient outcomes even after adjusting for the use of vasopressors to achieve these goals.^{29,30} Individual need may vary depending on baseline

blood pressure and severity of postarrest illness. Direct invasive monitoring of cerebral oxygenation and blood flow can reveal substantial interpatient heterogeneity (→ **Fig. 2**). Population-based hemodynamic goals may lead to hyperemic cerebral perfusion in some patients, theoretically worsening the risk of vasogenic edema or oxidative injury (see below) and clinically significant brain tissue hypoxia in others. Unfortunately, broadly applicable strategies do not yet exist to determine the optimal cerebral perfusion pressure for an individual patient as it changes over time, or alternatively to detect in real-time the presence of hyperemia or hypoperfusion.

Respiratory failure and dependence on mechanical ventilation are also common after CA, and imprudent ventilator management may potentiate secondary brain injury. Hyperventilation-associated hypocapnia may lead to cerebral vasoconstriction and exacerbate hypoperfusion, whereas normocapnia or even mild permissive hypercapnia are associated with improved neurologic outcomes.^{31,32} This effect relies on intact chemoregulation of cerebral blood flow, which may or may not be present after severe brain injury.³³ Because broadly applicable real-time measures of individual need and treatment responsiveness are not available, clinicians now treat individual patients using population-based estimates. Finally, severe hyperoxemia may increase oxidative stress through formation of reactive oxygen species, whereas hypoxemia causes unnecessary cellular hypoxia.^{34,35} In most patients, both hypocapnia and prolonged hyperoxemia are avoidable with careful ventilator management.

Cerebral Edema

Cerebral edema occurs early after ROSC in some patients or during rewarming in others, and regardless of timing is an

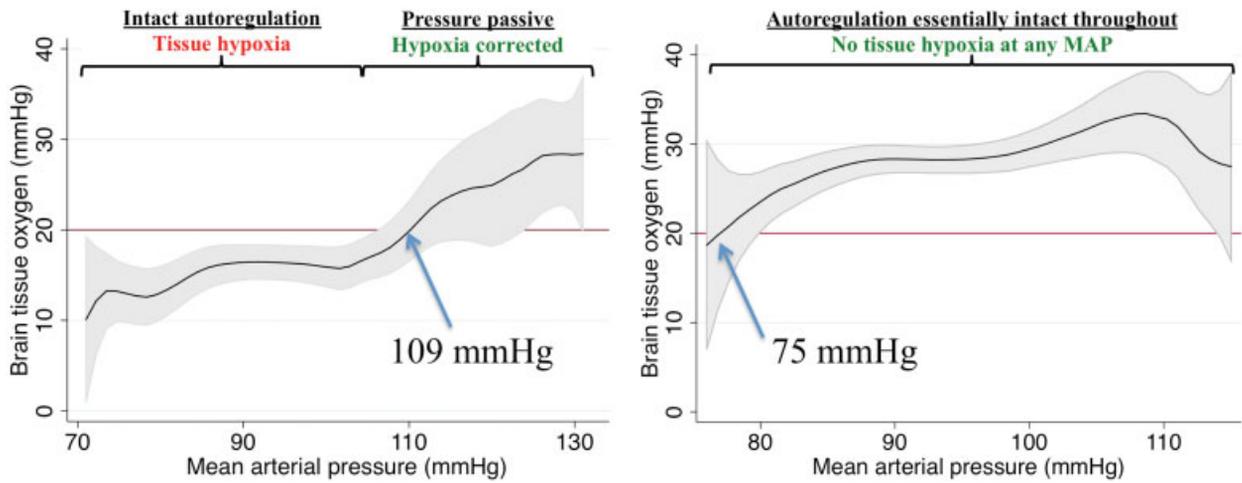


Fig. 2 Direct monitoring of brain tissue oxygenation or cerebral blood flow in two patients after cardiac arrest reveals significant between-patient variation in the necessary mean arterial pressure (MAP) to maintain adequate brain oxygenation. In the left panel, brain tissue hypoxia at a threshold of 20 mmHg (red line) is present despite intact autoregulation at blood MAPs below ~110 mmHg, but can be overcome by increasing MAP >110 mmHg. In the right panel, autoregulation is mostly intact and brain oxygenation is adequate across a range of MAPs.

ominous marker of severe brain injury. However, favorable outcomes can occur in patients with mild-to-moderate early edema.¹⁵ The timing of early cerebral edema and mechanistic studies suggest a vasogenic rather than cytotoxic mechanism for early edema,³⁶ and indeed hyperosmolar therapy may reduce radiographic signs of edema and intracranial hypertension (→**Fig. 3**). Reducing gross edema theoretically will improve microvascular blood flow to vulnerable brain regions, but it is unknown whether treating postanoxic cerebral edema improves patient outcomes.

Clinical Assessment of Brain Injury and Prognosis

Multimodal neurologic prognostication of coma after CA is also reviewed in detail in this issue. From the perspective of cerebral vulnerability after CA, it should be noted that inaccurate or inappropriately early neurologic prognostication after CA can

contribute substantially to avoidable mortality after CA.³⁷ Guidelines recommend delaying withdrawal of life-sustaining therapy based on neurologic prognosis until at least 72 hours after ROSC because the accuracy of prognostic information available prior to this time is limited.^{38–40} Even patients who remain comatose 72 hours after ROSC may go on to awaken and have favorable recoveries.⁴¹ Unfortunately, the withdrawal of life-sustaining therapy in the first 24 hours after ROSC based on perceived neurologic prognosis remains common.³⁷ Even the best postarrest critical care can be undermined by therapeutic nihilism and inappropriate care withdrawal.

Regional Heterogeneity Produces Different Brain Injury Phenotypes

Several neuronal subtypes and brain regions are particularly sensitive to the physiological and cellular effects of anoxic injury and circulatory arrest. This results in distinct

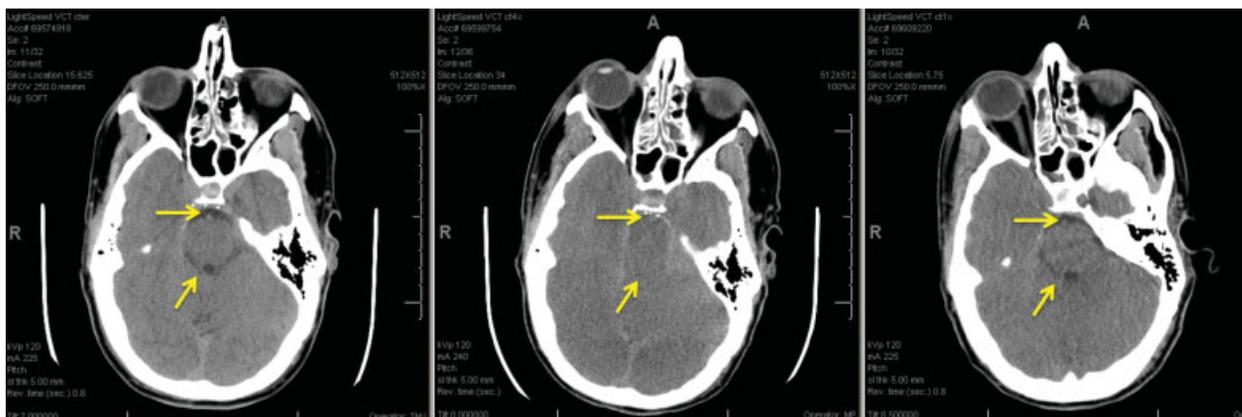


Fig. 3 Cerebral edema may develop early after cardiac arrest or during rewarming. In this patient, baseline computed tomography (CT) scan shortly after cardiac arrest was unremarkable (left). Just at the time of the second CT scan, the patient showed clinical signs of herniation, prompting empiric therapy with hypertonic saline. Basilar and quadrigeminal cisterns were collapsed (center, arrows). After 24 hours, the subject had recovery of brainstem reflexes and improved appearance on CT scan (right). Ultimately, this patient had no recovery of cortical function.

phenotypes among survivors of CA. For example, vulnerable cell populations include the hippocampal CA1 pyramidal neurons in the mesial temporal lobe.^{42,43} As a consequence, memory impairments, particularly the ability to consolidate short-term memory, are common after CA even among patients with otherwise favorable functional outcomes.^{44,45} Cerebellar Purkinje cell and basal ganglia injury with cortical sparing may lead to postanoxic myoclonus and a range of other movement disorders in patients who are cognitively intact.^{46–48} Cortical pyramidal neuron injury can cause impaired attention, processing speed, and/or executive function depending on the region of injury.^{44,45,49} Of note, many of these deficits also occur in patients with other critical illnesses who have not suffered CA, supporting the concern that a combination of critical illness, intensive care, and patient comorbidities can potentiate brain injury itself.^{50,51} Regardless, many patients experience substantial improvement in symptom severity in the months after CA, and rehabilitation improves recovery. Randomized trials have demonstrated that focused rehabilitation can improve social engagement, quality of life, and emotional outcomes as well as reduce medical complications in those discharged after CA.^{52,53}

Quantifying Neurologic Recovery

The common deficits described above are challenging to quantify. Indeed, most trials to date have relied on gross measures of functional or neurologic impairment such as Cerebral Performance Category (CPC) or modified Rankin Scale Score (mRS) as a primary outcome, in part because of their simplicity compared with more detailed neurocognitive testing (→ **Table 1**). In awake patients, CPC and mRS capture varying aspects of functional recovery across levels, and are influenced not only by the severity of illness, but also by environmental and personal factors that modify the interplay

between neurologic disability (e.g., arm paresis), activity (ability to carry out activities of daily living [ADLs]), and participation (ability to return to work).^{54,55} This means that the use of CPC or mRS as a primary trial outcome risks a failure to detect true physiological differences between treatment arms because of environmental or personal modifiers. These scales are dynamic over the course of recovery and sensitive to setting, adding an additional level of complexity when considering the timing of outcome assessment. For example, early after hospital discharge, functional measures may worsen as patients move from a sheltered hospital environment to home where there is less assistance for ADLs, then improve over the following 6 to 12 months.^{56,57} In addition, these scales are relatively insensitive to deficits in memory, executive function, and processing speed that develop commonly after CA and that are important to patient experience.^{45,58,59} More sensitive measures have been used and validated after CA, but have not thus far been implemented as clinical trial endpoints.^{45,50,59} Despite their limitations, short-term measures of functional recovery at hospital discharge do predict long-term survival. Those discharged with moderate or severe disability as measured by CPC are at substantially higher hazard of death compared with those with mild or no disability.⁶⁰

Conclusion

Post-CA brain injury results in multiple molecular and physiological changes over the hours to days after CPR. In practice, monitoring the status of the brain after CA and the prevention of secondary injury are central organizing principles for postarrest care. Reducing the deleterious effects of impaired homeostasis guides blood pressure and ventilator, fluid, and temperature management, as well as neurophysiological monitoring during postarrest intensive care. Proper multimodal assessment of

Table 1 Commonly used measures of neurologic recovery after cardiac arrest

Modified Rankin Scale	Cerebral Performance Category
0– <u>No symptoms at all</u>	1–Good recovery: Conscious, alert, able to work, might have mild neurologic or psychological deficit.
1– No significant disability despite symptoms; <u>able to carry out all usual duties and activities</u>	2–Moderate disability: Conscious, sufficient cerebral function for independent activities of daily life. <u>Able to work in sheltered environment</u>
2– Slight disability; <u>unable to carry out all previous activities, but able to look after own affairs without assistance</u>	3–Severe disability: Conscious, dependent on others for daily support because of impaired brain function; ranges from ambulatory state to severe dementia or paralysis
3– Moderate disability; <u>requiring some help, but able to walk without assistance</u>	4–Coma or vegetative state: Any degree of coma without the presence of all brain death criteria
4– Moderately severe disability; <u>unable to walk without assistance and unable to attend to own bodily needs without assistance</u>	5–Death: Apnea, electroencephalographic silence, etc.
5– Severe disability; <u>bedridden, incontinent, requiring constant nursing care and attention</u>	
6– Death: <u>Apnea, electroencephalographic silence, etc.</u>	

Note: Cerebral Performance Category and modified Rankin Scale measure different aspects of recovery. Neurologic impairments are listed in bold, function capability is in italics, and participation ability is underlined.

coma is critical to avoid premature withdrawal of life support resulting in death. The pattern of brain injury that remains after intensive care varies from mild to severe, with some brain regions being particularly susceptible. Proper evaluation of cognition and other functions after emergence from coma is critical for guiding postacute rehabilitation and support services. Traditional outcome scales (MRS, CPC) may be too coarse to detect cognitive issues that affect patients' quality of life.

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