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Review

Extracerebral multiple organ dysfunction and interactions with brain injury after cardiac arrest

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Abstract

Cardiac arrest and successful resuscitation cause whole-body ischemia and reperfusion, leading to brain injury and extracerebral multiple organ dysfunction. Brain injury is the leading cause of death and long-term disability in resuscitated survivors, and was conceptualized and treated as an isolated injury, which has neglected the brain-visceral organ crosstalk. Extracerebral organ dysfunction is common and is significantly associated with mortality and poor neurological prognosis after resuscitation. However, detailed description of the characteristics of post-resuscitation multiple organ dysfunction is lacking, and the bidirectional interactions between brain and visceral organs need to be elucidated to explore new treatment for neuroprotection. This review aims to describe current concepts of post-cardiac arrest brain injury and specific characteristics of post-resuscitation dysfunction in cardiovascular, respiratory, renal, hepatic, adrenal, gastrointestinal, and neurohumoral systems. Additionally, we discuss the crosstalk between brain and extracerebral organs, especially focusing on how visceral organ dysfunction and other factors affect brain injury progression. We think that clarifying these interactions is of profound significance on how we treat patients for neural/systemic protection to improve outcome.

Keywords: Cardiac Arrest, Post-Cardiac Arrest Brain Injury, Multiple Organ Dysfunction, Organ Crosstalk

Introduction

Cardiac arrest (CA) is the sudden loss of heart pumping function, resulting in the cessation of systemic blood flow. After successful cardiopulmonary resuscitation (CPR), return of spontaneous circulation (ROSC) is achieved. CA and ROSC cause complete whole-body ischemia and reperfusion, leading to post-cardiac arrest brain injury (PCABI) and extracerebral multiple organ dysfunction (EMOD).[1] PCABI is one of the key pathophysiological processes after resuscitation, and is the leading cause of death and long-term disability.[1–4] EMOD is common and heterogenous after resuscitation and is associated with significant mortality, but specific description of characteristics is lacking.[1,5] The dysfunction of one organ can lead to the dysfunction of other organs through inter-organ crosstalk, in which one organ failure influences the functions of others. However, PCABI has historically been conceptualized and treated as an isolated injury which neglected the brain-visceral organ interactions, and the impacts of life-threatening EMOD on the development of PCABI don't seem to receive sufficient attention.

In this review, we briefly introduce current concepts of PCABI. Additionally, we describe specific characteristics of post-resuscitation EMOD, including dysfunction/failure in cardiovascular, respiratory, renal, hepatic, adrenal, gastrointestinal, and neurohumoral systems. Finally, we put an emphasis on discussing the crosstalk between PCABI and EMOD, especially focusing on how EMOD and other factors affect PCABI progression Box 1.

Box 1 Summary of search strategy and paper selection.
We searched PubMed with the terms "cardiac arrest", "post cardiac arrest syndrome", "post-resuscitation", "brain injury", and "post-cardiac arrest brain injury" and relevant section topics (brain, heart, lung, liver, kidney, adrenal gland, gastrointestinal tract, gut, immune, endocrine, hormone, bladder, spinal cord, pancreas, adipose tissue, reproductive organ, multiple organ dysfunction). There were no language restrictions. We selected publications in the past 15 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of relevant articles identified by this search strategy and selected those we judged relevant. The final references were generated on the basis of their relevance to the topics covered in this Review.

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PCABI

PCABI is an acute hypoxic-ischemic brain injury primarily caused by cerebral ischemia/reperfusion injury deteriorated by systemic ischemia/reperfusion response. Neuronal subpopulations in hippocampus, cortex, cerebellum, corpus striatum, and thalamus are selectively vulnerable.[1] Clinical manifestations of PCABI include coma, seizures, myoclonus, cerebral edema, sympathetic hyperarousal, and neurobehavioral dysfunction.[1,6] Successful cerebral resuscitation without neurological deficits is the ultimate goal, however, no therapeutic has shown a clear association with improved survival and neurological outcome.[3,7–8]

PCABI: A part of post-cardiac arrest syndrome

Even victims successfully resuscitated, the morbidity and mortality remain significantly high due to a complex combination of pathophysiological processes termed as post-cardiac arrest syndrome (PCAS).[1] The most severe shock state during arrest (no-flow) initially causes systemic ischemia injury, additional hypoperfusion injury occurs after initiation of CPR (low-flow) and secondary injury continues to occur after ROSC (reflow) (Fig. 1). PCAS is a heterogeneous syndrome as multiple mechanisms contribute to injury with varying intensity within patients. It's worth noting that although PCAS is by definition of a combination of pathophysiological processes, it should not be construed as a simple superposition of organ dysfunction/failure which may neglect the internal pathophysiological mechanisms and importance of organ-organ crosstalk.

The four key components of PCAS comprise PCABI, post-cardiac arrest myocardial dysfunction (PCAMD), systemic ischemia/reperfusion response, and persistent precipitating pathology (Table 1).[1] Systemic ischemia/reperfusion response has many features in common with sepsis, including endotoxemia, systemic inflammation, activation of coagulation, hyperglycemia, and increased risk of infection.[1,6,7,9] All organ systems are at risk of getting dysfunctional or damaged by systemic ischemia/reperfusion. Persistent precipitating pathology represents the unresolved pathological process that caused the CA.[1] Pathophysiology, clinical findings, and treatment of these persisting acute pathology vary in individual patients with disease-specific features,[10] which can be an important source of heterogeneity.

Pathophysiology of PCABI

The pathophysiology of PCABI could be vividly summarized as a "two-hit" model, encompassed by primary ischemia injury and secondary injury following initiation of resuscitation.[3,4,11]

During CA, delivery of oxygen and energy substrates is completely halted. Brain is highly vulnerable to ischemia on account of high metabolism and poor energy storage, and clinical loss of consciousness occurs within 30 s.[12] Cessation of blood flow results in the shortage of cerebral energy generation and dysfunction of energy-consuming ion pumps. Ion homeostasis subsequently gets disturbed, further causing cell swelling and intracellular acidosis. Anoxic depolarization, the hallmark of ischemic brain injury, leads to opening of voltage-gated ion channels, after which Ca^{2+} moves into the cell and excitatory neurotransmitters like glutamate release causing excitotoxicity. Excitotoxicity and calcium overload lead to mitochondrial dysfunction, production of reactive oxygen species, and activation of lytic enzymes, causing cell damage and death. Moreover, this cell death could cause sterile inflammation (Fig. 2).

Secondary brain injury begins with resuscitation and lasts for days after ROSC.[1,3] Timely reperfusion prevents irreversible brain death, however, can also independently induce further damage. The key mechanism is an imbalance in cerebral oxygen delivery and utilization.[11] A wide range of pathological processes contribute to secondary injury, including blood–brain barrier disruption, microcirculation disturbance, impaired cerebrovascular autoregulation,

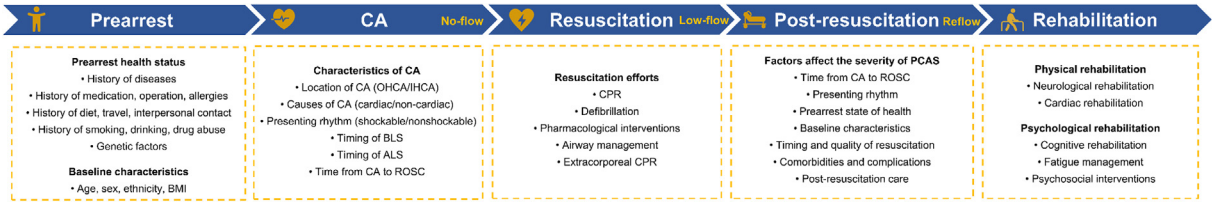

Fig. 1 – Development of PCAS: from prearrest status and CA to resuscitation, post-resuscitation status, and rehabilitation. The whole development process of PCAS could be identified as five stages: prearrest stage, during CA stage (no-flow state), resuscitation stage (low-flow state), post-resuscitation care stage (reflow state), and rehabilitation stage. Prearrest health status and basic characteristics constitute basic physiological conditions of patients, which have a significant impact on characteristics of subsequent stages. CA represents the most severe shock state, during which circulation is completely halted and systemic primary ischemia injury occurs. Characteristics of CA are considered as important source of heterogeneity in PCAS patients. After initiation of resuscitation, systemic hypoperfusion cause secondary injury. The cornerstones of resuscitation efforts are chest compression, ventilation, and early defibrillation. ALS like pharmacological interventions, airway management, and extracorporeal CPR contribute to improve ROSC, but may also affect PCAS. After ROSC, PCAS will occur and systemic secondary injury continues. PCAS is by definition of a complex combination of pathophysiological processes and is heterogeneous. The aim of post-resuscitation care is to improve survival, neurological outcome, and health-related quality of life by provide systemic and organ-specific protections. Cerebral resuscitation, which means survival with no neurological deficit, is the ultimate goal. Combination of physical and psychological rehabilitation is used to promote recovery at rehabilitation stage. ALS indicates advanced life support; BLS, basic life support; BMI, body mass index; CA, cardiac arrest; CPR, cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PCAS, post-cardiac arrest syndrome; ROSC, resumption of spontaneous circulation.

Table 1 – Clinical manifestations, pathophysiology, and mechanisms of key components of PCAS.

	PCABI	PCAMD	SIRR	PPP
Clinical manifestations	Coma, cerebral edema and elevated ICP, seizures and myoclonus, delirium, sympathetic hyperarousal, fever, neurobehavioral dysfunction, brain death	Hypotension, ventricular dysfunction, cardiogenic shock, reduced cardiac output, arrhythmias, pulmonary edema, recurrent arrest	Intravascular hypovolemia, hypotension, impaired oxygen delivery and utilization, vasoplegia, endotoxemia, relative adrenal insufficiency, hyperglycemia, increased risk of infection, SIRS/MODS	Disease-specific features
Pathophysiology and mechanism	"Two-hit" model • Primary ischemic injury: cessation of O_2 and energy supply, dysfunction of ion pumps, disturbance of ionic homeostasis, anoxic depolarization, excitotoxicity, calcium overload, cell swelling, cell damage and death, sterile inflammation • Secondary brain injury: global cerebral IRI, imbalance in O_2 delivery and use, inflammation, oxidative stress, calcium overload, mitochondria dysfunction, activation of cell-death signaling pathways, BBB disruption, microcirculation disturbance, impairment of cerebrovascular autoregulation, hypoxemia/hyperoxia, hyperpyrexia, hyperglycemia, seizures and myoclonus, delirium, cerebral edema, elevated ICP, reduced cerebral perfusion, electrolyte disturbance, effects of pharmacology, effects of medical interventions, neurodegeneration	Myocardial stunning/acute coronary syndrome, myocardial IRI, oxidative stress, calcium overload, cytokine mediated cardiovascular dysfunction, catecholamines-induced injury, electric shocks-induced injury	Sepsis-like syndrome: Systemic IRI, activation of immunologic pathways, elevated cytokines, endothelial activation, activation of coagulation/inhibition of anticoagulation, adequate activation of fibrinolysis/inhibition of antifibrinolysis	Disease-specific features

BBB indicates blood-brain barrier; ICP, intracranial pressure; IRI, ischemia/reperfusion injury; MODS, multiple organ dysfunction syndrome; PCABI, post-cardiac arrest brain injury; PCAMD, post-cardiac arrest myocardial dysfunction; PCAS, post-cardiac arrest syndrome; SIRR, systemic ischemia/reperfusion response; SIRS, systemic inflammatory response syndrome

inflammation, seizures and myoclonus, cerebral edema, and elevated intracranial pressure. Additionally, therapies that focus on individual organs may compromise other organs, therefore, pharmacotherapy and medical interventions (cardiac catheterization, mechanical circulatory support, mechanical ventilation, fluid resuscitation, nutrition) could contribute to the development of brain injury.

Monitoring, treatment, and prognostication

Given the complexity of PCABI pathophysiology, multimodal monitoring, a summary of neuromonitoring technologies in intensive care units (ICU) mainly used to detect and manage secondary brain injury, has been used and proved to improve care and outcomes of neurocritically ill patients.[13] Comprehensive, accurate, and timely monitoring is to the benefit of quantitative assessment of physiological changes and is directly related to the treatment strategy, especially it is significant for indicating the intervention sites and the intensity.

Management bundle of PCABI includes etiological treatment, general intensive care management, initial management of respiration and circulation, neuroprotection, and transport to CA centers.[7] To date, there is no effective pharmacological treatment for PCABI.[3] Failure to identify promising pharmacologic approaches serves as a reminder to further investigate the fundamental mechanisms and develop novel drug targets.

Prognostication in PCABI population can be challenging. Predicting good[14] and poor[15] neurological outcome, with both high sensitivity (true positive rate) and high specificity (true negative rate), is important for physicians to make correct decisions including continuation of therapy, withdrawal of life-sustaining therapy, and consideration of organ donation procedure. Given that no single predictor is entirely accurate, multimodal neuroprognostication strategy using clinical examination, electrophysiology, biomarkers, and imaging is recommended.[3,7] Additionally, delayed neurologic improvement in PCABI patients with poor neurological status at discharge was observed, indicating the need for prolonging observation period for neurological recovery and refinements of prognostication strategy (Table 2).[16,17]

EMOD after resuscitation and interactions with PCABI

EMOD is a severe life-threatening complication with large heterogeneity after resuscitation, but detailed description of characteristics

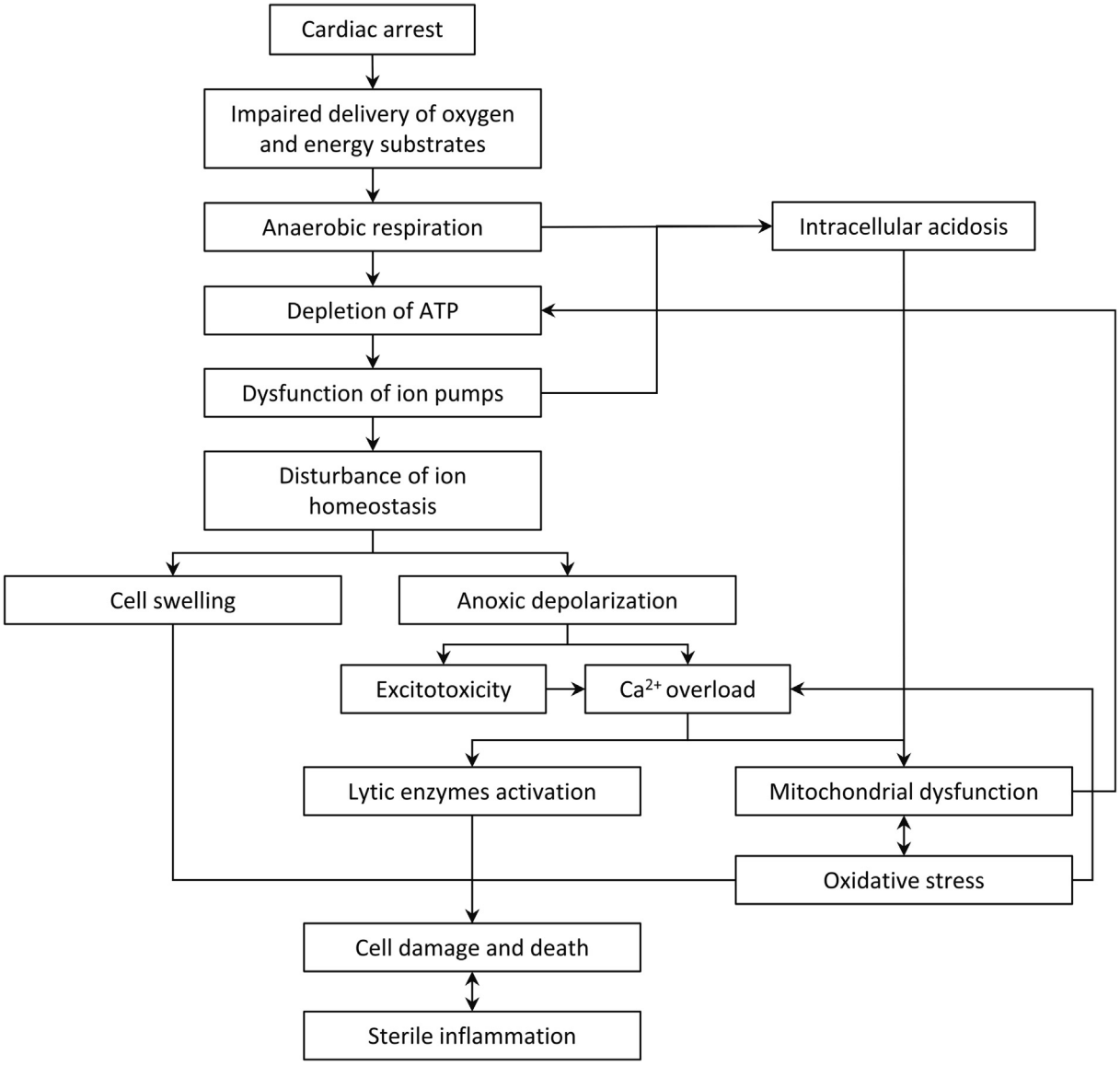

Fig. 2 – Schematic illustrating the proposed mechanism of primary injury of PCABI. CA causes complete cessation of oxygen and energy substrates for brain metabolism, and subsequently anaerobic respiration occurs, leading to lactate production and depletion of adenosine triphosphate (ATP). Energy-dependent ion pumps get dysfunction and results in disturbance of ion homeostasis, further leading to cell swelling, intracellular acidosis, and anoxic depolarization. After which, excitatory neurotransmitters get released and calcium moves into cells. Intracellular calcium overload leads to mitochondrial dysfunction and production of reactive oxygen species, which in turn aggravates this anoxic cascade. Additionally, calcium overload could activate lytic enzymes. Taken together, these pathophysiological processes together mediate the biochemical process of cell damage and death in primary cerebral ischemia injury.

is lacking. Dysfunction/failure of peripheral life-sustaining organs is primarily caused by ischemia and hypoperfusion during CA/CPR, and subsequently get aggravated by reperfusion with hemodynamic instability and oxygen cascade impairment after ROSC.[5] There are structural and functional connections between brain and visceral organs, through which the bidirectional interactions between PCABI and EMOD occur. Therefore, PCABI should not be conceptualized and treated as an isolated organ injury, and the role and contribution of EMOD in the development of PCABI is not clearly understood. Reducing the risk of EMOD and supporting extracerebral organ function if necessary are fundamental and effective measures for cerebral resuscitation, and patient-specific pathophysiology underlying EMOD must be considered in clinical practice and future studies for PCABI. Understanding these pathophysiological interactions may contribute to identify therapeutic targets of pharmacological interventions.

Neuroendocrine adaptions and relative adrenal insufficiency

CA/resuscitation causes severe stress cascade based on neuroendocrine responses, including activation of the hypothalamic–pituitary–adrenal axis, the sympathetic-adrenomedullary system, and

Table 2 – Monitoring, treatment, and prognostication strategy for PCABI.

	Monitoring	Treatment	Prognostication
Content	Multimodal monitoring • Continuous EEG • ICP monitoring • Cerebral hemodynamics • Cerebral oxygen • Cerebral microdialysis	Management bundle • Transport to CA centers • Etiological treatment • General intensive care management • Initial management of circulation • Initial management of respiration • Multiple organ protection/support • Neuroprotection o Control of seizures o Temperature control o No effective pharmacology	Multimodal neuroprognostication • Clinical examination • Pupillary light reflex • Corneal reflex • Quantitative pupillometry • Glasgow Coma Scale Motor score • Myoclonus • Imaging • CT • MRI • Electrophysiology • EEG • SSEP • Biomarkers • Neuronal cell body: NSE and UCH-L1 • Axon: NfL and Tau • Glia: GFAP and S-100B

CA indicates cardiac arrest; CT, computed tomography; EEG, electroencephalogram; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; NfL, neurofilament light chain; NSE, neuron-specific enolase; PCABI, post-cardiac arrest brain injury; SSEP, somatosensory evoked potentials; UCH-L1, ubiquitin carboxy-terminal hydrolase L1

renin-angiotensin-aldosterone system. Paroxysmal sympathetic hyperactivity, which is associated with unfavorable neurological prognosis, as well as enhanced parasympathetic activity, may be present in PCABI patients.[18] These post-CA neurohumoral changes initially have protective benefits, but also carry enormous risks to cause cerebral/systemic injury.

Relative adrenal insufficiency, clinically defined as a failure to respond to adrenocorticotropic hormone stimulation test (cortisol increase <9 μg/dl at 30 or 60 min compared to baseline concentration), is common in PCABI patients but frequently remains undiagnosed.[19–22] Relative adrenal insufficiency is associated with higher mortality and worse neurologic outcome,[20,22–24] PCAS patients who died of early refractory shock had inadequate adrenal response with lower baseline cortisol levels than patients who died of neurologic dysfunction.[25,26] Plasma total cortisol level increased, whereas glucocorticoid receptor expression and cell counts of lymphocytes rapidly decreased in the early state after ROSC.[27] Three major pathophysiologic components were considered to constitute adrenal insufficiency: dysregulation of the hypothalamic–pituitary–adrenal axis, altered cortisol metabolism, and tissue resistance to glucocorticoids, resulting in a general effect of decreased cortisol production.[28] The poor outcome observed in PCABI patients with corticosteroid insufficiency calls into question of corticosteroid supplementation in the event of post-resuscitation shock.[20] Using available but limited high-quality data could not directly analyze the association between corticosteroids and mortality in PCAS. In view of insufficient evidence to support or refute the use of corticosteroids in PCAS patients, the ERC-ESICM post-resuscitation care guidelines 2021 suggests that steroids are not given routinely until there is higher-certainty evidence supportive of use.[7] Additionally, the critical illness-related corticosteroid insufficiency guideline 2017 suggests using corticosteroids in the context of CA (conditional recommendation) owing to potential benefits.[29] The STEROHCA trial showed that administration of high-dose glucocorticoid immediately after ROSC was safe, reduced systemic level of inflammation, and improved post-resuscitation hemodynamics, but failed to reduce biomarkers of PCABI.[30,31] Future randomized controlled studies with a large sample size are needed to evaluate the relationship between administration of steroids and outcomes and complications in PCABI patients, as well as administration time (during and/or after CA), dosage, and ideal medication combinations.

PCAMD

The definition of PCAMD is important, however, there is no standard definition of PCAMD.[1,6,7,32] The clinical definition of PCAMD should be based on cardiac function monitoring, which plays a central role in diagnosis. Echocardiography and invasive monitoring with a pulmonary artery catheter could quantify PCAMD and indicate trends,[7] and evidence of reversible contractile dysfunction is required for diagnosis. The left ventricle ejection fraction (usually $<50\%$) is the most commonly used indicator, however, the threshold used as a definition of PCAMD is unclear.[32]

PCAMD-induced circulatory failure is the leading cause of early death.[1,10,33,34] Manifested as hypotension and systolic/diastolic dysfunction, PCAMD is both responsive to therapy and reversible, indicating the pathophysiology is myocardial stunning (except for acute coronary syndrome with more complicated pathophysiology) characterized by long-lasting (hours to days) contractile dysfunction as a consequence of myocardial ischemia/reperfusion injury.[1,6,34–38] Myocardial stunning resulting from oxidative stress and intracellular calcium overload[39] can lead to cardiogenic shock, reduced cardiac output, arrhythmias, pulmonary edema, and recurrent arrest. PCAMD usually recovers withing 72 h,[32] and its severity is related to the duration of CA.[6] Mechanisms of PCAMD include myocardial ischemia/reperfusion, cytokine mediated cardiovascular dysfunction, and secondary myocardial injury induced by catecholamines or electric shocks.[6,32] The neurogenic heart injury, including inflammation, central autonomic dysregulation, catecholamine release, structural myocardial changes, and vascular wall abnormalities has been revealed in focal cerebral ischemia injury,[40] but the influence of global cerebral ischemia injury like PCABI on myocardial injury and vice versa remains poorly understood.

The development of PCABI can be impacted by PCAMD due to the bidirectional link between heart and brain. PCAMD is a part of

post-resuscitation shock,[32] and PCAMD-induced low cardiac output could affect distant organs perfusion including reducing cerebral blood flow. Hemodynamic instability, such as hypotension caused by PCAMD, could reduce the cerebral perfusion pressure and further reduce the partial pressure of brain tissue O_2, exacerbating the imbalance between oxygen delivery and use. Therefore, maintaining adequate perfusion pressure is a fundamental part of goal-directed post-resuscitation care. Taken together, monitoring and treatment of PCAMD, for restoring and maintaining hemodynamic stability and delivery of oxygen to reduce early death, may create a window for neuroprotection and cerebral resuscitation, which have benefits on improving survival and neurological outcome.

Acute respiratory distress syndrome and pneumonia

Newly developed acute respiratory distress syndrome (ARDS), clinically defined with the Berlin definition and characterized by arterial hypoxemia and bilateral radiographical opacities, is common in PCAS patients, nearly half of out-of-hospital CA survivors developed ARDS and in-hospital CA survivors have a higher incidence.[41–44] ARDS after CA is associated with lower survival, poorer neurological outcome, and more consumption of medical resources.[42–44]

Multiple risk factors are involved in the development of ARDS after resuscitation. PCAS patients are in a state of immunosuppression as mentioned above, therefore, they are susceptible to infection[45] and pulmonary infection is most common, which accounts for 50% of cases.[46] Early-onset pneumonia is associated with longer duration of mechanical ventilation and ICU stay.[47] Pulmonary contusion can occur as a result of chest compressions during CPR, and CA/ROSC cause ischemia/reperfusion injury on lung tissue. Special CA conditions with primary pulmonary diseases, trauma, major operations, emergency and severe diseases, malignancy, drug toxicity, smoke inhalation, and drowning can also result in ARDS. In consideration of the organ crosstalk, lung injury could develop from and interact with acute distant organ injury in brain, heart, kidney, and gut.[48] Given that systemic inflammatory response in PCAS is a sepsis-like state and non-pulmonary sepsis is a common cause of ARDS, it is reasonable to assume that CA/CPR is a risk factor for ARDS.

Brain-lung crosstalk is a bidirectional interaction which plays an important role in critical illness including PCAS.[49] Primary brain injuries could trigger secondary lung injuries, including ARDS, neurogenic pulmonary edema, and ventilator-associated pneumonia.[50] Lung injury could also predispose to other organ dysfunctions including brain.[48,51] Respiratory dysfunctions (hypoxemia, hyper/hypocapnia, impaired respiratory system mechanics, dyspnea, asynchronies), inflammation (release of inflammatory mediators and neurotoxic factors, recruitment of inflammatory cells, activation of epithelium and endothelium), and adverse events of mechanical ventilation are among the mechanisms, predisposing factors, and tentative hypothesis of injury from lung to brain.[49–52]

Management of PCABI with lung injury could be complex. Airway management method, oxygen targets, carbon dioxide targets, ventilation strategy in PCABI complicating ARDS are still uncertain with great challenge.[7] Meticulous attention to ventilation and respiratory parameters may be associated with improved outcomes of CA,[53] and use of protective ventilatory strategies might prevent ARDS and improve outcomes.[54] A more precise post-resuscitation care for cerebral/systemic protection could be derived from early prediction the onset of ARDS, early intervention for respiratory infection and dysfunction, and prevention of refractory infection and anoxia. Prophylactic antibiotics therapy is controversial in post-resuscitation care. ERS-ESICM guidelines 2021 do not recommend using prophylactic antibiotics routinely on account of no overall benefits and increased risk of resistant organisms development.[7,55] While AHA/NCS statement suggests using empirical antibiotics to reduce the incidence of pneumonia.[56] From our point of view, we think that early prophylactic antibiotics is a reasonable therapy. The concerns of developing antibiotic resistance are important, but many patients may die before this due to organ failure. Early infection may induce sepsis and worsen outcome, and reducing the risk of infection-induced organ dysfunction may also protect remote organ systems from dysfunction by organ-organ crosstalk. Thus, early prophylactic antibiotics may increase the likelihood of intact neurological survival, and this concept need to be tested in future studies. Further refinements are needed to better understand ARDS in PCAS and determine how to effectively manage lung-associated brain injury.

Acute kidney injury

Acute kidney injury (AKI), defined by and categorized with the Kidney Disease: Improving Global Outcomes criteria that uses increased plasma creatinine level and decreased urine output as standards, is a common complication after resuscitation, which occurred in about 50% of PCAS patients.[57–61] AKI occurs at an early stage after ROSC.[57] Post-resuscitation AKI is associated with mortality and poor neurological outcome,[60,62–64] and recovery from AKI is a potent predictor of favorable neurological outcome.[57] PCABI patients with AKI exhibit more severe hemodynamic instability and need more aggressive therapy,[61,63] which is associated with increased use of mechanical ventilation and renal replacement therapy.[65] Preexisting cardiac or renal conditions, high lactate level, use of vasopressors, systolic blood pressure,[60,63] along with aging, male gender, longer resuscitation duration, post-resuscitation shock, and non-shockable rhythm,[61,62] are associated with severe AKI.

Clinical observations and preclinical studies have shown that AKI in PCAS is not an independent event, it may be the cause, outgrowth, or concurrent of other organ injury.[66] There are complex organ interactions between kidney and distant organs including brain, and damaged kidneys can have a detrimental effect on the central nervous system. Uremic toxins, water and electrolyte imbalance, acid/base imbalance, inflammation, oxidative stress, drug accumulation, dialysis disequilibrium syndrome, and neurohormonal dysfunction are among the factors underlying injury from kidney to brain.[67–70] These factors can cause uremic encephalopathy, and increase subsequent risks of cerebrovascular disease, cognitive impairment, and dementia.[67] Elucidating the intricate interactions between kidney and brain might result in novel diagnostics and therapies to improve outcomes in PCABI patients with AKI.

The high incidence and early development of AKI in PCABI patients reinforces the necessity for routine systematic surveillance at the admission to ICUs, along with early identification and control of risk factors, which have potential to decrease morbidity and mortality.[65,71] The use of urine and serum markers for diagnosis and/or prognosis of post-resuscitation AKI was investigated, but these markers have evident limitations in clinical utility,[72] indicating the necessity for seeking more precise biomarkers or establishing a comprehensive evaluation system encompassing a variety of parameters.

Acute gastrointestinal injury

There are few studies on alterations in gastrointestinal function in PCAS patients, characteristics of acute gastrointestinal injury after

resuscitation are not well described.[73–75] Gut dysfunction/injury, with elevated markers of injury and increased intestinal permeability, has been shown to be correlated with the presence of endotoxin in plasma after resuscitation.[73,74] Post-resuscitation intestinal injury is associated with EMOD and significant mortality, associated risk factors involve duration of CA, serum lactate level, and amount of adrenaline.[76]

Diagnosis of gastrointestinal injury with imaging methods can be challenging, whereas gastrointestinal endoscopy is not routinely performed after resuscitation.[7] Data of the incidence and severity of this gastrointestinal injury are sparse, but the actual data may be surprisingly high. A prospective study showed that more than 50% of successful resuscitated out-of-hospital CA patients had upper gastrointestinal tract ischemia injury (ulceration, necrosis, mucosal edema, erythema) that determined by endoscopy.[76] Severe gastrointestinal ischemia injury is associated with severe EMOD and worse neurological outcome, and presence of which is associated with adrenaline dose.[76] Another retrospective study showed about 60% PCAS patients have clinical signs of gastrointestinal dysfunction/injury, and endoscopic lesions (hemorrhage, necrosis, ulcer) were observed in all of whom underwent endoscopies.[74] Histologically, development and extension of subepithelial Gruenhagen's space, loss and necrosis of villi, destruction and ulceration, and inflammation of mucus are observed in CA/CPR animal experiments.[77–79] It is recommended to administer stress ulcer prophylaxis in post-resuscitation care.[7] CA-induced ischemia, PCAMD-induced hypotension, and epinephrine can cause non-occlusive mesenteric ischemia, causing injuries ranging from cell dysfunction to transmural necrosis, which rarely occurs but is associated with extremely high mortality and unfavorable neurological outcome.[80,81] Additionally, post-resuscitation intestinal microcirculation decreased significantly with increased duration of CA, and this microcirculatory disturbance is closely correlated with PCAMD and systemic inflammation.[82] Moreover, gastrointestinal complications raise the question of the feasibility, safety, and clinical efficacy of early enteral feeding after ROSC. Evidence of this issue is limited, and the ERC-ESICM guidelines recommended to start low-rate gastric feeding and low-dose enteral feeding, which may be tolerated.[7]

The concept of a microbiota-gut-brain axis has been well established, through which gut and brain can influence each other.[83] This axis is a network involving gut microbiome, enteric nervous system, enteric neuroendocrine system, and gut-associated immune system.[84] The bidirectional interactions between brain and gut occur through three parallel but interconnected pathways: neuronal pathway (vagus nerve and dorsal root ganglia), humoral pathway (immune factors and hypothalamic–pituitary–adrenal axis), and cellular immune pathway (stress-induced alteration of microbiome and activation of immune cells, inflammatory immune cells migrate to brain, activation of brain-resident immune cells by signaling molecules from gut microbiota).[85] The gut is regarded as the motor of critical illness including sepsis and EMOD, which are states similar to systemic inflammatory response in PCAS.[86] Therefore, it is not surprising that gut dysfunction/lesions could contribute to or be associated with the development and severity of PCABI. Additionally, the gut microbiota can signal to the nervous system via three categories of signaling molecules: food-related metabolites (metabolites of amino acids, polysaccharides, polyphenol like neurotransmitters, polyamines, short-chain fatty acid, serotonin, estrogens), immune signaling (intact microbes and microbial cell wall components like lipopolysaccharide), and metabolites of endogenously produced molecules (like bile acids and active hormone metabolites).[83,84] However, how gut microbiota changes after CA/CPR, how these changes affect development of PCABI/PCAS and outcomes, and what are the underlying mechanisms remain poorly understood and need to be investigated. Taken together, combined effects of increased intestinal permeability, alterations in gut microbiome, increased apoptotic epithelium, altered mucus integrity, and formation of toxic gut-derived lymph are proposed to propagate inflammation driving distal organ injury including PCABI.[86]

How the functional change and damage occur in gut, the timing course and heterogeneity of injury in different sections, how these changes affect the core outcome set for CA, and the underlying mechanisms remain poorly understood. The role of gut in the development of PCABI/PCAS should not be ignored, and more emphasis needs to be placed on the investigation from bench to bedside since the gut may be a potential therapeutic target for cerebral/systemic protection in post-resuscitation care.

Hypoxic liver injury

Hypoxic liver injury, defined by an elevation of alanine aminotransferase over 20 times the upper limit of normal, is a common and life-threatening complication after resuscitation.[87–89] This acute liver injury is caused by hypoxia (ischemia, passive congestion, arterial hypoxemia), and is pathologically characterized by centrilobular liver cell necrosis with fatty degeneration at the border.[90] Duration of CA and multifactorial effects are associated with the development of acute liver disfunction.[87,88,91]

The incidence of hypoxic liver injury is about 10% after resuscitation,[88,89,91,92] which might be underestimated, because it might occur beyond 72 h after resuscitation,[87] and patients might die due to organ failure before this. This liver injury is strongly associated with poor neurological outcome and significant mortality (up to 80% of the deaths).[88,89,91,92] The significant correlation between acute liver injury and unfavorable neurological outcome suggests that liver dysfunction has a profound negative impact on brain in the setting of CA. However, hardly any research has sought to investigate and unravel underlying mechanisms. The imbalance of oxygen supply and demand in liver results in cell death, subsequently metabolic disturbance and damage effect could lead to cerebral and systemic inflammation (release of inflammatory mediators), coagulopathy, and hepatic encephalopathy (alterations in ammonia metabolism).[93] Predicting and monitoring the liver function may be useful in preventing further cerebral/systemic damage. Even if demonstrating this problem may still be a long way off, researchers are laying the foundation for discovery and there are still many issues that need to be resolved (Fig. 3).

Conclusions and future directions

PCABI is the leading cause of mortality and morbidity after resuscitation. No therapeutic-related factors have shown a clear association with improved survival and neurological outcome after CA to date. The mechanisms associated with PCABI remain elusive, although the "two-hit" model partly generalize the intracranial pathophysiology. CA/ROSC cause complete systemic ischemia and reperfusion, leading to EMOD which is significantly associated with mortality and poor neurological outcome. There is complex crosstalk among organs, therefore, PCABI should not be conceptualized and treated as an isolated injury in consideration of the interactions between EMOD. The role of EMOD in the progression of PCABI need to be evaluated

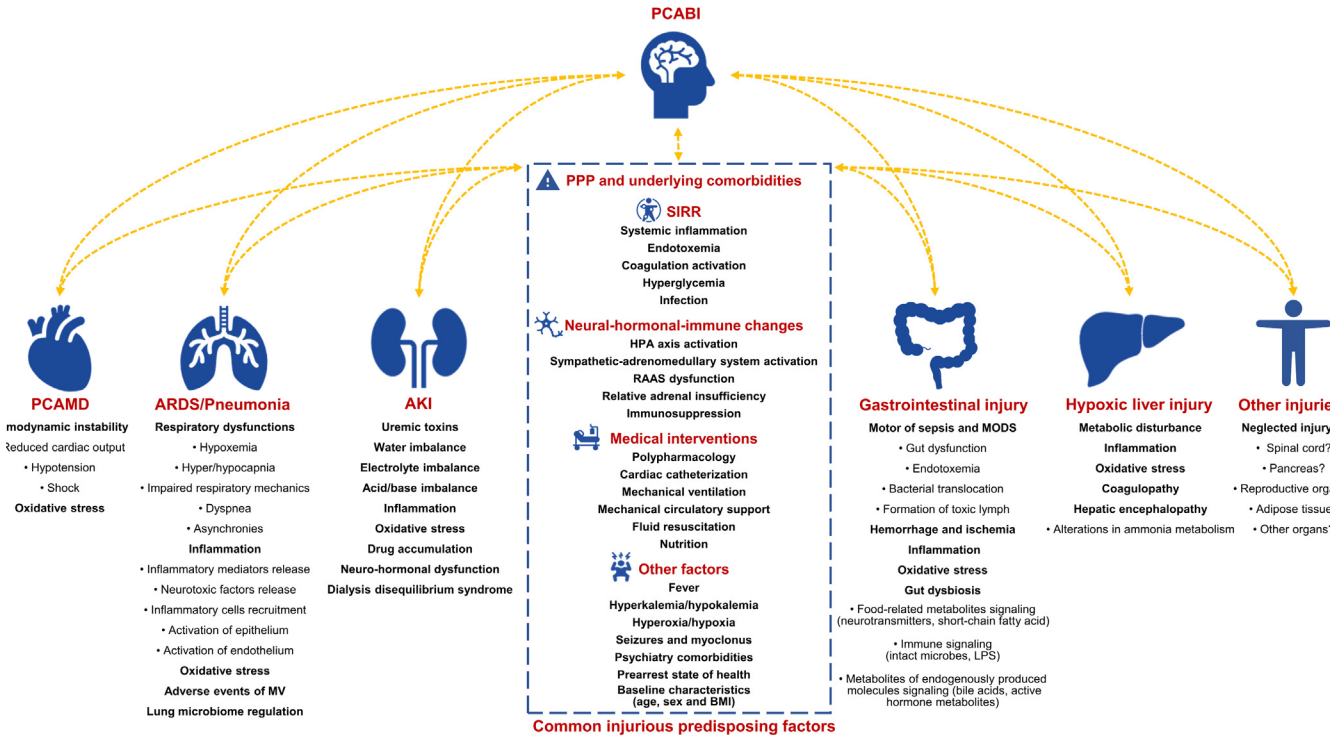

Fig. 3 – EMOD after CA and affects PCABI development through the bidirectional brain-visceral organ crosstalk. EMOD after CA is common and heterogeneous, and is associated with significant mortality and unfavorable neurological outcome. Common injurious predisposing factors, including persistent precipitating pathology, systemic ischemia/reperfusion, neurohumoral-immune changes, medical interventions, and other factors, could affect the development of PCABI and EMOD. There exist bidirectional interactions between brain and visceral organs, through which injurious factors of PCAMD, ARDS and pneumonia, AKI, gastrointestinal injury, hypoxic liver injury, and other organ dysfunction/failure contribute to PCABI development. PCABI should not be conceptualized and treated as an isolated organ injury, reducing the risk of EMOD and supporting extracerebral organ function if necessary are fundamental and effective measures for neural/systemic protection and cerebral resuscitation. AKI indicates acute kidney injury; ARDS, acute respiratory distress syndrome; BMI, body mass index; EMOD, extracerebral multiple organ dysfunction; HPA, hypothalamic–pituitary–adrenal; LPS, lipopolysaccharide; MODS, multiple organ dysfunction syndrome; MV, mechanical ventilation; PCABI, post-cardiac arrest brain injury; PCAMD, post-cardiac arrest myocardial dysfunction; PCAS, post-cardiac arrest syndrome; PPP, persistent precipitating pathology; RAAS, renin-angiotensin-aldosterone system; SIRR, systemic ischemia/reperfusion response.

and elucidated. Multiple mechanisms of EMOD and other factors can contribute to PCABI development, and their relative contributions might be the source of heterogeneity and define distinct PCABI/PCAS subtypes. Elucidating these interactions and internal mechanisms is of profound significance on exploring novel treatments for organ protection and cerebral resuscitation, as well as guiding future research. Future studies should define distinct phenotypes of PCABI/PCAS based on mass high-quality raw data, and explore corresponding mechanisms, from which optimized diagnostic and therapeutic strategies could be explored. It is reasonable to speculate that all organ systems get dysfunction from complete ischemia/reperfusion, and clinical observation is important to ascertain if particular organ dysfunction is neglected or nonexistent. We should take therapeutic strategies including patient-centered holistic and individual therapy strategy, along with integral therapy strategy focused on the pathophysiologic mechanism of crosstalk among organs. Opposite treatment strategies could occur in PCABI complicating EMOD, therefore, a pragmatic and multidisciplinary approach should guide the often-difficult decision-making in clinical practice given the limited evidence. We need to consider the advantages and disadvantages of therapeutic in each organ separately, and actively coordinate the interactions between brain and visceral organs, adding new treatments if necessary. Monitoring and treatment should be administered at early phase after resuscitation, potential therapeutic interventions may provide extensive/specific organ protection for reducing early mortality and create a window for cerebral resuscitation to improve neurological outcome.

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Zhun Yao: Writing – original draft, Visualization, Methodology, Conceptualization. **Yuanrui Zhao:** Methodology. **Liping Lu:** Methodology. **Yinping Li:** Writing – review & editing, Funding acquisition. **Zhui Yu:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

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