

Available online at [ScienceDirect](https://www.sciencedirect.com)

# Resuscitation

journal homepage: [www.elsevier.com/locate/resuscitation](https://www.elsevier.com/locate/resuscitation)EUROPEAN  
RESUSCITATION  
COUNCIL

## ILCOR Scientific Statement

# Improving Outcomes After Post-Cardiac Arrest Brain Injury: A Scientific Statement From the International Liaison Committee on Resuscitation <sup>☆</sup>

*Gavin D. Perkins, Robert Neumar, Cindy H. Hsu, Karen G. Hirsch, Anders Aneman, Lance B. Becker, Keith Couper, Clifton W. Callaway, Cornelia W.E. Hoedemaekers, Shir Lynn Lim, William Meurer, Theresa Olasveengen, Mypinder S. Sekhon, Markus Skrifvars, Jasmeet Soar, Min-Shan Tsai, Bhuma Vengamma, Jerry P. Nolan, on behalf of the International Liaison Committee on Resuscitation*

### Abstract

This scientific statement presents a conceptual framework for the pathophysiology of post-cardiac arrest brain injury, explores reasons for previous failure to translate preclinical data to clinical practice, and outlines potential paths forward. Post-cardiac arrest brain injury is characterized by 4 distinct but overlapping phases: ischemic depolarization, reperfusion repolarization, dysregulation, and recovery and repair. Previous research has been challenging because of the limitations of laboratory models; heterogeneity in the patient populations enrolled; overoptimistic estimation of treatment effects leading to suboptimal sample sizes; timing and route of intervention delivery; limited or absent evidence that the intervention has engaged the mechanistic target; and heterogeneity in postresuscitation care, prognostication, and withdrawal of life-sustaining treatments. Future trials must tailor their interventions to the subset of patients most likely to benefit and deliver this intervention at the appropriate time, through the appropriate route, and at the appropriate dose. The complexity of post-cardiac arrest brain injury suggests that monotherapies are unlikely to be as successful as multimodal neuroprotective therapies. Biomarkers should be developed to identify patients with the targeted mechanism of injury, to quantify its severity, and to measure the response to therapy. Studies need to be adequately powered to detect effect sizes that are realistic and meaningful to patients, their families, and clinicians. Study designs should be optimized to accelerate the evaluation of the most promising interventions. Multidisciplinary and international collaboration will be essential to realize the goal of developing effective therapies for post-cardiac arrest brain injury.

**Keywords:** AHA Scientific Statements, acute brain injuries, cardiopulmonary resuscitation, post-cardiac arrest syndrome, rehabilitation, resuscitation

Cardiac arrest remains a common, devastating event for patients and their families.<sup>1–3</sup> Data from 11 national and 4 regional registries encompassing the United States, Europe, Asia, and Australasia suggest that the annual incidence of emergency medical service–treated cardiac arrests is between 30 and 100 per 100 000 population.<sup>4</sup> Initial resuscitation efforts are effective at achieving a return of spontaneous circulation (ROSC) at hospital handover in  $\approx 1$  in every 3 to 4 patients, although rates vary within and between countries.<sup>5–7</sup> Among those admitted to intensive care, many will later die in hospital because of post-cardiac arrest brain injury.<sup>8</sup> Many of these patients die after withdrawal of life-sustaining treatment after a diagnosis of presumed irreversible severe brain injury based on prognostic tests. The Core Outcome Set for Cardiac Arrest initiative highlights the importance

that patients, their families, and clinicians place on longer-term, patient-focused outcomes.<sup>9,10</sup> Survival without neurological impairment, enabling the person to resume their pre-cardiac arrest level of function, remains the overarching goal of resuscitation.

The treatment of cardiac arrest and its sequelae consumes substantial health and social care resources.<sup>11–13</sup> Although improvements have occurred in the early links of the chain of survival (activation of emergency response,<sup>14,15</sup> high-quality cardiopulmonary resuscitation [CPR],<sup>16,17</sup> defibrillation, and advanced life support<sup>18,19</sup>), progress in developing therapeutic interventions to address post-cardiac arrest brain injury and recovery has been stagnant.<sup>8,20,21</sup> The 2020 Advanced Life Support Consensus on Science and Treatment Recommendations covered 32 topics, of

<sup>☆</sup> This article has been copublished in *Circulation*.

<https://doi.org/10.1016/j.resuscitation.2024.110196>

0300-9572/© 2024 by the European Resuscitation Council, American Heart Association, Inc., and International Liaison Committee on Resuscitation. Published by Elsevier B.V. All rights are reserved.

which only 6 related to postresuscitation care interventions to reduce post-cardiac arrest brain injury. Among the 6 topics (oxygen dose after ROSC, mechanical ventilation strategies, hemodynamic support, use of corticosteroids, seizure prophylaxis and treatment, and targeted temperature management), there was no moderate- or high-certainty evidence to support the effectiveness of any interventions to reduce post-cardiac arrest brain injury. The lack of progress in the treatment of post-cardiac arrest brain injury remains a barrier to the International Liaison Committee on Resuscitation achieving its vision of saving more lives globally through resuscitation.<sup>22</sup>

The aim of this scientific statement is to present a conceptual framework for the pathophysiology, classification, and phases of post-cardiac arrest brain injury; to explore reasons for previous failures to translate preclinical discoveries to clinical practice; to consider what preclinical data are required to justify future human clinical trials; and to outline potential paths forward that mitigate previous limitations. Barriers to the discovery and translation of neuroprotective therapies for post-cardiac arrest brain injury were identified and prioritized with modified Delphi methods. This scientific statement makes recommendations for preclinical study end points, real-time monitoring, and clinical trial design for early-phase efficacy and proof-of-concept trials and explores promising clinical therapies and future treatments across a range of times and settings. The scientific statement is set in the context of patients' and families' experiences to shine a spotlight on the urgent need for progress in this area (survivor and family stories). The International Liaison Committee on Resuscitation hopes that this scientific statement will help researchers, clinician scientists, and funders advance the field for the treatment of post-cardiac arrest brain injury.

## POST-CARDIAC ARREST BRAIN INJURY MECHANISMS

### A Survivor's Story

*Trouble with the brain is it doesn't know when to switch itself off. Trouble with my heart is it did. On Sunday 6th March 2022 at 10:17 pm, that's exactly what happened. After playing football for around 90 minutes, I felt something that I can't remember. First a heart attack, then a cardiac arrest. Dead. For 52 minutes. Two hospital doctors were kitted up for footie but scrubbed up well to take it in turns to administer CPR for that time to allow an ambulance crew to shock me, more times than I care to remember, back to existence. Alive.*

*I was in a coma for 8 days, and when I came 'round I couldn't move my legs and was in the midst of ICU [intensive care unit] delirium. My brain ached. Coping with the physical impact was tough; learning how to walk again, feed myself, write, visit the toilet unaided. However, the mental impact is incessant and relentless. I've had mental lows bordering breakdowns but can run for hours. They say I've had a miraculous recovery—they are not wrong, but they are wrong. My brain aches, not like the merciless east winds that knife us, but rather like the incessant and relentless pain of not knowing. It's cold in the dark.*

*Dr Muhammed Asad Jayani (survivor)*

### Brain Injury Mechanisms

Cardiac arrest followed by CPR and ROSC may trigger a sequence of brain injury mechanisms that are complex and incompletely understood. On the basis of available evidence, we propose a mechanistic construct that includes 4 sequential and at times overlapping phases aligned with temporal stages of disease progression and treatment. These phases include (1) ischemic depolarization, (2) reperfusion repolarization, (3) dysregulation, and (4) recovery and repair (Table 1 and Figure 1). Within each phase are multiple, potentially causal mechanisms that occur to varying degrees according to severity of injury, response to injury, and treatment at the individual, organ, and cellular levels.

It is well established that subpopulations of cell types in the brain have different vulnerabilities to post-cardiac arrest brain injury, but the mechanisms of this selective vulnerability are poorly understood.<sup>23,24</sup> Specific events or thresholds that cause the transition from reversible to irreversible injury remain unknown but may potentially be modifiable.<sup>25,26</sup> These brain-specific injury mechanisms also interact with the systemic effects of total body ischemia and reperfusion, as well as with the persistent precipitating pathologies.

### Ischemic Depolarization

Ischemic depolarization, also called direct current shift or terminal depolarization, is caused by multiple complex pathways and mechanisms, including inadequate brain oxygen delivery, cessation of oxidative phosphorylation, ATP depletion, failure of plasma membrane ion pumps, loss of plasma membrane potential, opening of voltage-gated ion channels, excitatory neurotransmitter release, opening of ligand-gated ion channels, and reversal of plasma membrane ion pumps, leading to equalization of ion gradients across the plasma membrane.<sup>27,28</sup> During ischemic depolarization, intracellular calcium increases from the nanomolar to micromolar range, causing pathological activation of proteases (calpains), phosphatases (calcineurin),<sup>29</sup> and phospholipases (phospholipase A2).<sup>30–32</sup> Intracellular sodium overload contributes to fluid shifts from the cerebrospinal fluid and extracellular space to the intracellular space, causing cytotoxic edema.<sup>33</sup> Last, anaerobic glycolysis produces lactate, carbon dioxide (CO<sub>2</sub>), and hydrogen ions, decreasing pH.

In preclinical models, cortical ischemic depolarization occurs when cerebral blood flow (CBF) drops below a threshold of 10 mL·min<sup>-1</sup>·100 g<sup>-1</sup> or <20% of normal brain blood flow.<sup>34,35</sup> After sudden cessation of blood flow, ischemic depolarization occurs within 2 to 5 minutes.<sup>36,37</sup> The duration of ischemic depolarization after which capacity for neuron recovery is lost remains unknown. However, recent animal studies suggest that it could be up to 1 hour when conditions of reperfusion are optimized.<sup>38,39</sup> The CBF required to reverse ischemic depolarization is greater than the threshold at which ischemic depolarization first occurs and increases the longer ischemic depolarization is left untreated.<sup>34</sup> When preclinical data are translated to clinical practice, it follows that early CPR has the potential to prevent or delay ischemic depolarization, although the CBF achieved by CPR may not be sufficient to reverse established ischemic depolarization, especially if the onset of CPR is delayed. Ultimately, ischemic depolarization must be reversed for neurons to survive.

### Reperfusion Repolarization

Reperfusion repolarization requires CBF to return to a level that provides sufficient oxygen delivery to restore mitochondrial ATP synthe-

**Table 1 – Theoretical Construct for Post-Cardiac Arrest Brain Injury Mechanisms**

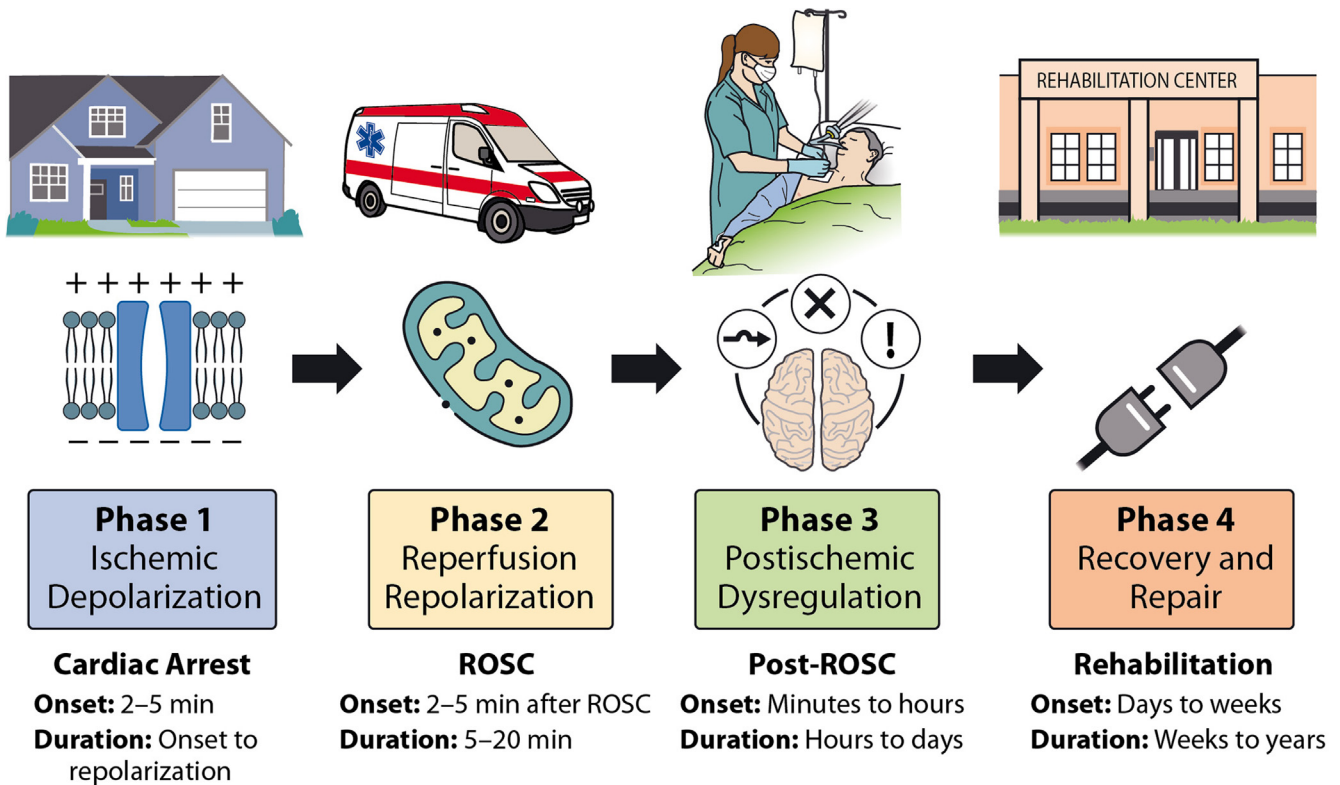
Mechanistic Phases			
Ischemic Depolarization	Reperfusion Repolarization	Dysregulation	Recovery and Repair
Cardiac arrest	ROSC	Post-ROSC	Rehabilitation
Onset: 2–5 min after arrest	Onset: 2–5 min after ROSC	Onset: Minutes to hours after ROSC	Onset: Days to weeks after ROSC
Duration: onset to repolarization reperfusion	Duration: 5–20 min	Duration: hours to days	Duration: weeks to years
Potential Causal Mechanisms			
Proteases Phosphatases Phospholipases Cell swelling Acidosis Intravascular thrombosis	Mitochondrial Ca <sup>2+</sup> overload Mitochondrial superoxide production Mitochondrial permeability transition Neutrophil extracellular traps No-reflow	Secondary brain tissue hypoxia Excitotoxicity Endothelial dysfunction Blood-brain barrier disruption Brain edema (vasogenic and cytotoxic) Disrupted Ca <sup>2+</sup> homeostasis Mitochondrial dysfunction Protein synthesis inhibition Altered gene expression Pathologic proteases Pathologic inflammation	Recovery of regulation Neurogenesis Synaptic plasticity

ROSC indicates return of spontaneous circulation.

sis by oxidative phosphorylation, membrane ion gradients by membrane ion pumps, and resting membrane potential below the threshold for opening of voltage-gated ion channels. Although essential for neuronal survival, reperfusion repolarization can also cause harm. During initial reperfusion, hyperpolarization of the inner mitochondrial membrane potential also causes the mitochondrial matrix to buffer excess cytosolic calcium through the mitochondrial Ca<sup>2+</sup> uniporter.<sup>40</sup> This buffering function can both uncouple ATP synthesis and cause superoxide production, which can be exacerbated by tissue hypoxia during initial reperfusion. Moreover, mitochondrial matrix calcium overload can trigger opening of the mitochondrial permeability

transition pore.<sup>41</sup> Permanent mitochondrial permeability transition pore opening causes failure of mitochondrial energy production and can lead to cell death. Transient mitochondrial permeability transition pore opening can trigger release of apoptosis-inducing factor and cytochrome C, which are triggers for apoptosis.

After prolonged cardiac arrest, regional tissue reperfusion can be impaired after ROSC by microvascular thrombosis, endothelial edema, and formation of neutrophil extracellular traps. In such cases, there is ongoing tissue ischemia rather than reperfusion repolarization. The regional reperfusion deficits after restoration of CBF (no reflow) have been observed in multiple species.<sup>42,43</sup> The involved



**Figure 1 – Mechanistic phases of post-cardiac arrest brain injury. ROSC indicates return of spontaneous circulation.**

territories of reperfusion defect increase with the duration of ischemia. Elevating the reperfusion blood pressure or replacing blood with saline before reperfusion can ameliorate the no-reflow defect in animals.<sup>44</sup>

In preclinical models, reperfusion repolarization occurs within 2 to 5 minutes of ROSC, and the associated superoxide production and mitochondrial matrix  $\text{Ca}^{2+}$  overload resolve within 15 to 20 minutes.<sup>45,46</sup> The time course for resolution of regional malperfusion has not been well delineated. These findings suggest that there may be a narrow therapeutic window for targeting reperfusion repolarization injury mechanisms and underscore the importance of targeting the appropriate mechanistic pathophysiology at the appropriate time point.

### Dysregulation

The dysregulation phase of post-cardiac arrest brain injury begins minutes to hours after ROSC and lasts for hours to days. The mechanisms underpinning additive tissue injury during this phase can be approached systematically by considering components of the neurovascular unit. The neurovascular unit, which is the principal site of neuronal homeostasis, is composed of the cerebral microvascular endothelium, blood-brain barrier, neurons, and surrounding glial cells.<sup>47</sup> The mechanisms contributing to the pathophysiology during dysregulation include postresuscitation brain tissue hypoxia (arising from a failure of both oxygen delivery and oxygen uptake), neuronal excitotoxicity, mitochondrial dysfunction, pathogenic inflammation, and microvascular dysfunction. In addition to these mechanisms that occur at a cellular level, regional and global changes in perfusion and oxygenation are deranged during this time, likely reflecting a complex interplay between cell-level changes and macrovascular dysregulation.

### Secondary Brain Tissue Hypoxia

Post-ROSC brain tissue hypoxia is associated with widespread injury to the cellular components of the neurovascular unit, including astrocytes, neuron cell bodies, and

axons.<sup>48</sup> Although mitigation of brain tissue hypoxia is possible by optimizing cerebral oxygen delivery, biological or clinical efficacy has not been clearly demonstrated with mean arterial pressure augmentation alone, thereby highlighting the importance of the diffusion and utilization stages of the oxygen cascade.<sup>49–51</sup> The mechanisms responsible for such observations in humans are likely related to derangements in cellular metabolism. Reduced middle cerebral artery blood flow velocity has not been associated with an anaerobic state of cerebral metabolism, thereby raising the possibility that reductions in CBF may be coupled to a compensatory reduction in the cerebral metabolic rate of oxygen consumption during the dysregulatory phase.<sup>52</sup>

In postcapillary cerebral venules, neutrophil adhesion and aggregation with subsequent neutrophil extracellular trap formation can contribute to obstruction of postcapillary blood flow.<sup>53</sup> Collectively, these pathophysiological processes lead to dysfunctional microvascular blood flow control at the neurovascular unit and blood-brain barrier breakdown with ensuing vasogenic cerebral edema. In extreme cases, fulminant cerebral edema may be associated with decreased cerebral oxygen delivery and reduced oxygen diffusion, both of which can lead to significant additive neurological injury.<sup>48</sup>

Disrupted cerebrovascular autoregulation is also a potential contributor to secondary tissue hypoxia. In some cases, a transient increase in CBF (15–30 minutes) after ROSC is seen, and physiological perturbations in the microvasculature are characterized by oligemic CBF early after ROSC.<sup>54,55</sup> This period of oligemia may be followed by delayed dynamically heterogeneous hypoperfusion<sup>56</sup>

and dysfunctional autoregulation over the hours and days after cardiac arrest.<sup>57</sup> Some patients have altered cerebral autoregulation and increased intracranial hypertension, which may cause cerebral hypoperfusion, and secondary brain tissue hypoxia that could worsen post-cardiac arrest brain injury.<sup>48,58</sup> It is important to note that changes in autoregulation, as measured by the correlation between blood and intracranial pressure, are dynamic longitudinally and are linked to adverse outcomes.<sup>59</sup> In an observational setting, authors demonstrated that deviation below the optimal mean arterial pressure with a bedside autoregulation index was associated with reduced brain tissue oxygen tension,<sup>59</sup> and mean arterial pressure above the upper limit of autoregulation has also been associated with adverse outcomes.<sup>60</sup> However, there is a lack of prospective data demonstrating improved cerebrovascular physiological parameters (eg, brain tissue oxygenation or metabolism) with targeting the optimal mean arterial pressure.

#### *Neuronal Excitotoxicity*

Potential contributors to excitotoxicity during the dysregulation phase include excess glutamate release due to seizures and the interictal continuum; impaired glial cell uptake of extracellular glutamate; increased neuron sensitivity to glutamate because of altered glutamate receptor subtype expression, impaired energy, and calcium metabolism; and loss of inhibitory interneurons.<sup>61–63</sup> The potential net result is delayed secondary intracellular and mitochondrial calcium overload, contributing to delayed neuronal death.<sup>64,65</sup>

#### *Mitochondrial Dysfunction*

There is likely significant heterogeneity in the cellular pathophysiology of mitochondrial dysfunction, including depletion of essential metabolic cofactors (ie, thiamine), intracellular calcium signaling, and formation of reactive oxygen species. Intracellular calcium accumulation is associated with numerous harmful effects on cellular integrity, including mitochondrial dysfunction and activation of lytic enzymes (proteases, phospholipases), which lead to the death of neurons and glia.<sup>8,20</sup>

#### *Inflammation*

An additional injury mechanism that has emerged in recent years is the concept of an immunopathological response to sterile injury during the dysregulation phase.<sup>20</sup> Animal studies suggest that microglia are activated after ischemia/reperfusion, and the release of proinflammatory cytokines into the neurovascular unit (eg, interleukin-1 $\beta$ , interleukin-18, interleukin-6) may promote programmed cell death in vulnerable neurons.<sup>66</sup> Furthermore, the nucleotide-binding oligomerization domain-like (NOD-like) receptor protein 3 inflammasome pathway with downstream signaling of interleukin-1 $\beta$  and initiation of cellular death has been demonstrated in a rat model of cardiac arrest.<sup>67</sup> Blocking this pathway with pharmacological inhibitors results in decreased microglia-induced neuron injury and death.<sup>67</sup> Aspects of microglial activation and the immune response may be adaptive and essential for clearing compromised cellular debris from neurovascular units and are needed for tissue repair. Future research should focus on evaluating the balance of adaptive and maladaptive immune system signaling to identify promising immunomodulatory targets.

The multiple mechanisms underpinning the dysregulation phase highlight the complex nature of the pathophysiological processes pertinent to post-cardiac arrest brain injury. These mechanisms are not well understood in vivo in the human brain, especially in

patients with ROSC after cardiac arrest, because current measurements of brain metabolism, oxygenation, and inflammation are limited, and those that do exist often cannot ascertain pathophysiology at the cellular level. Given the time window of the dysregulation phase, therapeutic targeting of these mechanisms is likely optimally instituted within minutes to the first 24 hours after successful ROSC. Immediate key future steps include demonstrating their presence in humans and conducting preliminary interventional studies to determine the modifiability of disease mechanisms before large clinical trials are undertaken.

#### *Recovery and Repair*

Brain recovery and repair start within days after the initial brain injury and can continue for weeks and months and probably longer. The obvious clinical manifestations are awakening and return of cognitive function and the longer-term improvements seen in survivors. The mechanisms in cardiac arrest survivors are poorly understood, and our understanding comes mainly from the brain remodeling that occurs after stroke.<sup>68</sup> Brain mechanisms related to functional recovery after ischemic brain injury include neuroplasticity and neurogenesis.

Neuroplasticity is the reorganization and remodeling that occurs between neurons to restore function by linking brain regions. This occurs by synaptic pruning in which dysfunctional synapses are lost and new synapses sprout.<sup>69</sup> Neurogenesis is the generation of new neurons from endogenous progenitor cells. Neurogenesis is tightly controlled in the healthy brain. Angiogenesis and neuroglial genesis occur in parallel to neurogenesis, and several mediators (eg, brain-derived neurotrophic factor, vascular endothelial growth factors) appear to be involved.<sup>70</sup> Neurogenesis has been observed in several brain regions after injury (eg, hippocampus, cortex).<sup>71–73</sup>

Neuroplasticity and neurogenesis can be both beneficial and harmful in terms of restoring function. For example, although brain injury can trigger the migration of progenitor cells to the area of injury, those cells may not develop into functioning neurons and may develop into dysfunctional neurons, causing long-term epilepsy.<sup>74</sup> Neuroplasticity and neurogenesis can potentially be influenced by pharmacological and nonpharmacological (eg, rehabilitation, exercise, sleep) interventions or by the use of exogenous stem cells.<sup>70,73</sup> The balance between repair and recovery and chronic degenerative processes triggered by the initial brain injury remains poorly understood, and better understanding of the balance between functional and dysfunctional repair mechanisms is needed.

#### *Need to Develop Mechanistic Biomarkers*

Ideally, clinical trials deliver therapies aimed at and titrated to a specific mechanistic pathology and administered at the correct time to engage the targeted mechanism. Unfortunately, we lack real-time mechanistic biomarkers (eg, blood-based, physiological monitoring, imaging) that identify patients with specific injury mechanisms and patterns, quantify injury severity, and can be used to measure response to therapy. The development of mechanistic biomarkers that are distinct from those typically used to measure neurodegeneration, which are not specific to mechanism, is a critical next step. Ideally, these biomarkers could be developed and validated in preclinical models, along with associated therapies, and then used in subsequent clinical trials to monitor mechanistic target engagement. Theoretical examples of this approach are illustrated in [Table 2](#).

## WHY HAS PRECLINICAL RESEARCH FAILED TO TRANSLATE TO CLINICAL PRACTICE?

### A Family's Story

*In April 2018, my sister suffered a cardiac arrest after blunt chest trauma. Her heart stopped and required resuscitation at the scene with CPR from paramedics. Upon revival, she was transferred to Vancouver General Hospital for further management. After being admitted to the intensive care unit, the medical team updated my family with regards to the management approach. Although the medical team was transparent regarding the supportive measures which would be undertaken to improve her chance of recovery, we were also struck by the paucity of available effective medical therapies for post-cardiac arrest brain injury. During the course of her intensive care admission, my sister suffered refractory status epilepticus for 8 weeks and required interventions aimed at quelling her seizures.*

*Nearly 5 years later, my sister's recovery and rehabilitation journey has been protracted with significant challenges, including long-lasting obstacles with respect to her functional, cognitive, and emotional impairments. This single traumatic incident has significantly diminished her quality of life. As my sister's primary caregiver, I can attest that post-cardiac arrest brain injury remains an enormous challenge for patients and caregivers. In particular, identifying effective medical therapies is pivotal to helping improve the long-term outcomes of patients (like my sister) suffering from this disease. Intuitively, understanding the disease and optimizing study designs as well as outcome assessment is imperative to inform future research. Having reviewed this manuscript, I believe that the authors have identified a well-defined path to accomplish these goals. It is my sincere hope that by following the path laid forth by the manuscript, the rapid identification of effective medical therapies is on the horizon, thus benefiting this heterogeneous population of patients and their families by improving the long-term outcomes and their quality of life.*

*Ms Carmen Choi (sister)*

### Limitations of Laboratory Models

In most preclinical studies, laboratory models are designed to test interventions in highly controlled conditions, with little variation in injury models, populations tested, and delivery of the therapy or intervention. In most cases, the studies are optimized to test a single intervention. This is critical for early-phase discovery, but it limits subsequent generalizability.

Some limitations of laboratory models include evaluation of the intervention in only a few species and at single centers, use of injury models that do not replicate clinical models, the costs and ethical challenges of testing the effects of interventions on long-term survival and recovery in animals, and the inadvertent introduction of confounders. One example of the last is seen in studies of global cerebral ischemia in dogs in which cardiopulmonary bypass is frequently used to restart the heart because the maximum duration of

ischemia after which dogs can be resuscitated by CPR alone does not cause severe brain injury.<sup>75</sup> The cardiopulmonary bypass is not intended to be part of the resuscitation intervention but instead is a strategy to provide a suitable post-cardiac arrest brain injury model. However, its inclusion in the research model introduces many sources of possible confounding. Another example is the use of anesthetics, which is required in animal studies of cardiac arrest and brain ischemia. Concerns for animal welfare mean that anesthetic drugs are typically given before cardiac arrest in animal studies. These drugs may interact both with the intervention studied and with the animal model itself. Studies in different injury mechanisms such as traumatic brain injury have shown that different anesthetics may be neuroprotective.<sup>76,77</sup> Thus, the use of anesthetics in the experimental animal model is necessary but also may be a source of bias.

Additional limitations of injury models include the method of inducing cardiac arrest. Animal models may use noncardiac arrest models of cerebral ischemia such as focal ischemia in stroke (middle cerebral artery occlusion models) or models of global ischemia (eg, neck tourniquet,<sup>78</sup> bilateral carotid occlusion, and 4-vessel occlusion in rodents<sup>79</sup>). These models are informative because they isolate the effects of intervention on brain ischemia that are independent of the systemic effects of cardiac arrest on other organs and may be informative for how the brain may respond to interventions during global ischemia or after reperfusion.<sup>80</sup> However, these examples also fail to incorporate the systemic illness that accompanies brain ischemia in clinical practice and therefore may not adequately replicate the injury pathways that occur in cardiac arrest.

Other common concerns in the interpretation of preclinical study results include potential risks of bias from unclear reporting of random assignment and lack of blinding.<sup>81,82</sup> Animal studies are not usually analyzed on an intention-to-treat principle; thus, we do not know how many animals were initially included to produce the results reported. This may increase the risk of selective reporting. The protocols of animal studies also are rarely published before the analysis; thus, protocols may evolve, and outcomes may change after the studies are done. Small sample sizes lead to important uncertainty in the interpretation of experimental results, and testing standardized injury severity limits the generalizability. Thus, animal studies often report large effect sizes that are unrealistic for the clinical setting and can result in overly optimistic power calculations and underpowered clinical studies.

The remainder of this section provides further information about the challenges of translating preclinical research into clinical trials using the populations, interventions, controls, and outcomes format, and examples of specific limitations related to preclinical populations/species and injury models are offered.

### Population

The animals used in experimental trials are generally homogeneous in breed, genetics, and environment, whereas the human cardiac arrest populations are much more diverse and complex, with a wider range of genetic, environmental, and lifestyle factors that may influence the effectiveness of the interventions being tested. A recent review of preclinical models of cardiac arrest identified >1700 animal studies published from 2011 through 2016.<sup>83</sup> Studies were conducted in multiple species, with the most common being pigs, rats, and mice, although the same study was not often performed across multiple species. This review highlighted many additional limitations in preclinical models: Only about half of the studies identified in this

**Table 2 – Examples of Mechanistic Translation**

Mechanistic Phase	Potential Causal Mechanisms	Potential Mechanistic Biomarkers	Potential Mechanistic Treatments
<b>Ischemic depolarization</b>	Early brain edema Thrombosis	Neuroimaging Blood biomarkers of thrombosis and thrombolysis	SUR1-TRPM4 inhibitors Anticoagulation, thrombolysis
<b>Reperfusion repolarization</b>	Mitochondrial superoxide production Mitochondrial permeability transition NETs	Blood biomarkers of oxidative stress Blood biomarkers of mitochondrial injury Blood biomarkers of NET formation	Hypothermia, antioxidants, free radical scavengers Calcium uniporter blocker, MPTP inhibitors, COX regulation DNase therapy
<b>Dysregulation</b>	Brain tissue hypoxia Excitotoxicity Inflammation Delayed brain edema	PbtO <sub>2</sub> monitoring EEG, NIRS, Transcranial doppler Blood biomarkers of inflammation Neuroimaging	Optimize CDO <sub>2</sub> (MAP, PaCO <sub>2</sub> , ICP, hemoglobin) Sedation and antiepileptic drugs Immunomodulation ICP treatment
<b>Recovery and repair</b>	Synaptic plasticity and neurogenesis	Neuroimaging, EEG, tractography	Exercise, sleep, nutrition, exogenous growth factors, stem cells

CDO<sub>2</sub> indicates cerebral oxygen delivery; COX, cyclooxygenase; DNase, deoxyribonuclease; EEG, electroencephalogram; ICP, intracranial pressure; MAP, mean arterial pressure; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NET, neutrophil extracellular trap; NIRS, Near Infra-Red Spectroscopy; PaCO<sub>2</sub>, partial pressure carbon dioxide; PbtO<sub>2</sub>, continuous brain tissue oxygen; SUR1-TRPM4, sulfonylurea receptor 1–transient receptor potential melastatin 4.

review focused on neurological outcomes; >50% of the studies included only male animals; and the cardiac arrest injury mechanism and resuscitation strategies varied greatly. The significant heterogeneity in preclinical studies of cardiac arrest highlights the challenges with comparing studies, synthesizing data across studies, and developing a unified pathophysiological pathway that is a reasonable mechanistic target for clinical research. Ideally, preclinical animal studies would engage populations that enable assessment of whether the intervention can reach its intended target and exert the expected mechanistic effect while being similar enough to humans to exhibit the mechanistic pathways relevant for the therapeutic intervention in clinical trials. Multicenter preclinical trials could improve the generalizability and robustness of research findings. The International Liaison Committee on Resuscitation calls on funders and investigators to combine resources to help transform the translational landscape for post-cardiac arrest brain injury.

### Intervention

There are several important differences between laboratory and clinical settings for delivering interventions to mitigate brain injury after cardiac arrest. In animals, the timing of delivery can be tightly controlled, and delivery typically occurs immediately after, or even before, the cardiac arrest or ROSC, with no or minimal variance. The timing plausibly makes time-sensitive pathophysiological processes maximally amenable to intervention. The route of delivery—for example, intravenous access or a secure airway—is often established before cardiac arrest, further minimizing any delay in delivering the intervention. The stable pharmacodynamics and pharmacokinetics in animals are conducive to reaching effective dosing, and high doses can potentially be used without concern for intermediate to long-term adverse effects. Translating these preclinical experimental doses from animals to equipotent doses in humans may be difficult.

The laboratory setting is also well controlled and constant in terms of environmental factors (eg, temperature, lighting, movements), staffing (eg, multiple tasks can be completed simultaneously by dedicated individuals), and ancillary resources (eg, even a complex level of monitoring is immediately available). In contrast, the clinical scenario is typically unpredictable and pharmacologically complex, with variable delays in establishing a means or route to begin any intervention, and it is often challenged by resource constraints.

### Comparator

Although most animal studies are undertaken by the same staff in a well-controlled single laboratory, clinical studies are often completed across multiple sites and countries and by staff of variable experience with the study protocol. Clinical trials must allow treating teams to act in the best interests of the patient. If a treatment assignment leads to better or worse intermediate states for a patient (eg, worse oxygenation or lower blood pressure in one group versus another), critical care interventions may be systematically different between control and treatment groups. If these ancillary interventions do affect outcomes, which is the belief and intent of the clinicians applying any intervention, there are systematic differences in clinical trials that do not exist in laboratory studies.

### Outcome

The outcome in preclinical studies is frequently assessed with histology, biomarkers, and animal-specific neurological deficit scores, whereas clinical trials generally use scale-based dichotomized functional outcomes as the primary study outcome. Differences in these assessment methods may at least partly account for failure of translation from preclinical to clinical studies. In clinical trials, withdrawal of life-sustaining treatment may reduce any treatment effect because patients may die despite receiving an effective therapy. This makes it difficult to translate the treatment effect obtained in animal studies to clinical trials. This can be mitigated by protocolizing and monitoring neuroprognostication and withdrawal of life-sustaining treatments.<sup>84,85</sup> Last, mortality in different species may result from species-specific sensitivity of organs to ischemia. After experimental models of cardiac arrest, comatose rodents may have airway secretions, audiogenic seizures, and impaired ventilatory reflexes that result in sudden death during recovery,<sup>86,87</sup> whereas dogs often

develop multiple organ failure and mesenteric ischemia.<sup>88</sup> Although airway obstruction and mesenteric ischemia can occur in humans after cardiac arrest, they are not common causes of recurrent cardiac arrest or post-cardiac arrest mortality.

## Case Examples of Therapeutic Interventions That Have Failed to Translate to Improved Outcomes in Clinical Trials

Many interventions that have shown improved outcomes in animal models of cardiac arrest have produced neutral results when studied in clinical trials. Selected examples of failures to translate promising results from preclinical to clinical studies are shown here and are linked to their relevant mechanistic phase (ischemic depolarization, reperfusion/repolarization, dysregulation, and recovery and repair), outlined above.

### Thiopental

Thiopental is an example of how, historically, therapies demonstrating benefit in animal cardiac arrest models were almost immediately studied in clinical settings. The story of barbiturates as a neuroprotective therapy after cardiac arrest provides important insights.<sup>78,89</sup> In 1978, a research group from the University of Pittsburgh published astounding results on the neuroprotective effects of thiopental after brain injury in 62 rhesus monkeys (Table 3).<sup>78</sup> The brain injury was caused by inducing hypotension (mean arterial pressure, 50 mm Hg) and applying a neck tourniquet to stop circulation to the brain. High doses of thiopental (90–120 mg/kg) were administered at 15, 30, and 60 minutes after release of the tourniquet, and the animals were then treated with intensive care for up to 7 days before euthanasia. The animals' neurological deficit was scored daily, and at the end of the experiment, the brains were assessed for histopathological injury. All 10 control animals were in various states of coma, whereas the thiopental-treated animals were largely able to walk, sit, and feed themselves. There were dose-response signals for which earlier administration and higher doses generally showed better results. Despite subsequent neutral animal studies, thiopental was being used in clinical cardiac arrest settings without any clinical trial data.

**Table 3 – Example of Failure to Translate From Preclinical to Clinical Trials for Thiopental**

	Preclinical <sup>78</sup>	Clinical <sup>89</sup>
<b>Population</b>	62 monkeys with 16-min hypotension and neck tourniquet	262 comatose cardiac arrest survivors
<b>Intervention</b>		
Target mechanism	Reduce ischemic injury Reduce cerebral edema	Reduce cerebral metabolism Reduce edema Reduce seizure activity
Timing	5, 15, 30, or 60 min after ischemia	Within 60 min of ROSC
Dose	Thiopental 90–120 mg/kg	Thiopental 30 mg/kg
<b>Control</b>	Standard ICU care for 7 d	Standard ICU care
<b>Outcomes</b>		
Clinical	Neurological deficit score decreased if thiopental delivered within 15 min at 90 mg/kg, extending to 60 min at 120-mg dose	Good cerebral recovery 20% in thiopental group vs 15% in control group
Mechanistic	Histopathology scores decreased ICP (no difference)	No biomarker for metabolism

ICP indicates intracranial pressure; ICU, intensive care unit; and ROSC, return of spontaneous circulation.

Supplemental Material provides expanded examples covering hypothermia, oxygen, and xenon.



The clinical trial published 8 years later in 1986 randomized 262 comatose survivors of cardiac arrest.<sup>89</sup> The trial was designed to detect a 20% improvement in survival with favorable outcome but reported neutral results with 20% versus 15% favorable outcome in intervention and control groups, respectively. The potential reasons for the failure of preclinical findings to translate to the clinical trial include the following: (1) Power calculations based on the animal experiment were highly optimistic; (2) the infusion of thiopental in the clinical trial was delayed compared with the time shown to be effective in the preclinical study; (3) the optimal dose for the clinical trial had not been defined; (4) the mechanism was not well defined, and therefore, it is unknown whether this was tested adequately in the clinical trial; and (5) the preclinical trial involved cerebral ischemia but not cardiac arrest.

### Hypothermia

Hypothermia for post-arrest neuroprotection is likely one of the most well-known interventions, and its journey through the preclinical and clinical space presents many learning opportunities. A systematic review and meta-analysis of randomized controlled animal studies comparing the effect of hypothermic temperature control with normothermia after resuscitation from cardiac arrest included 45 studies and 981 animals.<sup>90</sup> Animal species included rats (28 studies), pigs (14 studies), rabbits (2 studies), and dogs (1 study). There were broad differences in mean no-flow times, mean low-flow times, time to hypothermia induction, cooling rates, temperature targets, and duration. Despite the heterogeneity in the preclinical experimental models, the standardized mean difference in the neurological deficit score was  $-1.4$  (95% CI,  $-1.7$  to  $-1.1$ ), which indicates a strong favorable effect for hypothermic temperature control. Mortality in the hypothermia temperature control groups was reduced by 67% (odds ratio, 0.33 [95% CI, 0.24–0.45]) compared with the controls.

Clinical trials studying hypothermic temperature control have shown varying results. One randomized clinical trial<sup>91</sup> and 1 pseudo-randomized clinical trial<sup>92</sup> documented improved outcomes with mild hypothermia (32 °C–34 °C) in patients comatose after resuscitation from out-of-hospital cardiac arrest with an initial shockable rhythm. Two subsequent larger trials found no difference in all-cause mortality or 6-month functional outcome between groups. The first of these, the TTM-1 trial (Targeted Temperature Management), randomized to temperature control at 33 °C versus 36 °C for 24 hours,<sup>93</sup> whereas the TTM-2 trial compared a target temperature of 33 °C with targeted normothermia with early treatment of fever ( $\geq 37.8$  °C).<sup>85</sup> A small trial that compared temperature control at 31 °C and 34 °C also found no difference in outcomes.<sup>94</sup> In contrast, 1 study showed an increase in the proportion of patients with a favorable functional outcome in the group with hypothermic temperature control to 33 °C compared with the normothermia group,<sup>95</sup> with the result being driven largely by the in-hospital arrest population, who showed the most significant improvement in outcomes in the intervention arm. However, these findings were not replicated in the Hypothermia After Cardiac Arrest In-Hospital trial, leading to the early termination of the trial.<sup>96</sup>

The potential reasons why preclinical findings did not clearly translate across clinical trials include the following: (1) Power calculations based on optimistic preclinical effect sizes may overestimate effects achievable in clinical practice<sup>97</sup>; (2) the delivery of hypothermia in the clinical trials was delayed ( $\approx 5$  hours after ROSC to reach target temperature in most studies) compared with the time shown to be effective in the preclinical studies; (3) the optimal dose of hypothermia had not been defined; and (4) the mechanisms are

incompletely understood and likely worked through multiple pathophysiological pathways, and therefore, it is unknown whether it was tested in the right patients. Examples of failure to translate promising preclinical findings for intracardiac arrest hypothermia and post-ROSC hypothermia are given in [Supplemental Tables 1 and 2](#).

### Oxygen Targets

Oxygen targets after ROSC have been the subject of extensive preclinical experimental research and more recently tested in multicenter randomized controlled trials (RCTs). Insufficient delivery of oxygen (delivery of oxygen below the demand threshold) after ROSC compounds the hypoxic-ischemic injury sustained before ROSC, whereas excessive delivery of oxygen (delivery of oxygen above the demand threshold) may induce neuronal damage by increased oxidative stress, mitochondrial dysfunction, and the generation of reactive oxygen species.<sup>98–100</sup> Hyperoxia further evokes vasoconstriction and reduced CBF.<sup>101</sup> Although the identification and description of mechanistic pathways are largely based on preclinical studies, sufficient overlap in mechanistic biomarkers (eg, measurement of lipid peroxidation, DNA damage, or CBF) has not followed through to clinical trials.

In a systematic review of animal cardiac arrest studies comparing ventilation using 100% oxygen with ventilation using less oxygen or titrated to normoxemia, neurological deficit and neuronal damage were worse in animals receiving 100% oxygen.<sup>102</sup> The studies were conducted across multiple species (rats, dogs, and pigs) with considerable separation between inspired fractional oxygen and arterial oxygen tension once ROSC was achieved. Although these animal studies have important differences from the clinical setting in terms of pre-cardiac arrest ventilation, concurrent lung injury, the timing and duration of oxygen delivery, and adjunct therapies, as well as the lack of long-term outcomes, they demonstrate the mechanistic importance of hyperoxia. Observational studies have also supported a deleterious effect of hyperoxia in cardiac patients<sup>103</sup> and critically ill patients in general,<sup>104–106</sup> albeit with considerable heterogeneity between studies.

Clinical studies of conservative compared with liberal oxygen targets starting after ROSC in the prehospital setting<sup>107–109</sup> or in the ICU<sup>51,110</sup> have not reported adverse outcomes with a higher oxygen target. Given the role of reperfusion in the generation of reactive oxygen species, it seems likely that any harmful effects of hyperoxemia are likely more pronounced at the time of ROSC or soon after. In the multicenter, parallel-group EXACT clinical trial (Reduction of Oxygen After Cardiac Arrest), paramedics randomized patients with ROSC after out-of-hospital

cardiac arrest and titrated oxygen to achieve oxygen saturation measured by pulse oximetry (Spo2) of 90% to 94% (intervention) or Spo2 of 98% to 100% (standard care) en route to hospital and until the first arterial blood gas measurement was obtained in the ICU ([Supplemental Table 3](#)).<sup>111</sup> The study, stopped early because of COVID-19, found that 82 of 214 patients (38.3%) in the intervention group survived to hospital discharge compared with 101 of 211 (47.9%) in the standard care group ( $-9.6\%$  difference [95% CI,  $-18.9\%$  to  $-0.2\%$ ];  $P=0.05$ ). A hypoxemic episode (Spo2  $<90\%$ ) before ICU admission occurred more often in the intervention group compared with the standard care group. Neither the BOX RCT (Blood Pressure and Oxygenation Targets in Post-Resuscitation Care)<sup>110</sup> nor post hoc/subgroup analyses of the ICU-ROX study (Intensive Care Unit Randomized Trial Comparing Two Approaches

to Oxygen Therapy)<sup>112</sup> and HOT-ICU study (Handling Oxygenation Targets in the ICU)<sup>113</sup> found a significant association between hyperoxia during mechanical ventilation after cardiac arrest and poor neurological outcome or mortality at 3 to 6 months.

If the mechanistic importance of hyperoxia in animal models is to be translated to the clinical setting in humans, it is important to quantify suprphysiological oxygen values, to define a threshold value, and to establish whether there is a dose-response relationship. Hyperoxemia, that is, oxygen excess in blood (above-normal arterial partial pressure of oxygen [Pao<sub>2</sub>] of 75–100 mm Hg), should be distinguished from hyperoxia, that is, oxygen excess in tissues (eg, above-normal brain cortical continuous brain tissue oxygen [Pbto<sub>2</sub>] of ≈20–25 mm Hg). The best metric to define suprphysiological oxygen levels remains debated.<sup>114</sup> Both the metrics and the measurement principles of oxygenation need careful evaluation within and between animal and human studies. Robust preclinical evidence that hyperoxia is harmful after cardiac arrest remains to be translated to the clinical setting; the oxygen story highlights many methodological challenges of translating preclinical experimental intervention studies to clinical trials.

### Xenon

Xenon has been shown to be neuroprotective in various brain injury models over the past 20 years (cardiac arrest, traumatic brain injury, and stroke). A recent systematic review and meta-analysis suggested that it may reduce neurological injury by as much as one-third across various models and species.<sup>115</sup> Although the exact mechanism for the neuroprotective effects of xenon is not fully understood, a possible mechanism may be inhibition of the glycine site on the N-methyl-d-aspartate receptor, causing dysregulated neurotransmission and excitotoxicity.<sup>116</sup>

The safety and effectiveness of xenon as an anesthetic gas are well established in humans, but its cost and availability have likely been major barriers to testing xenon as a neuroprotective agent in clinical trials. A small clinical trial has shown feasibility and safety of a target mechanism (Supplemental Table 4).<sup>117,118</sup> Despite these preliminary results, subsequent clinical studies investigating the efficacy of xenon as a neuroprotective agent after cardiac arrest have stalled, and to the best of our knowledge, there are no active or planned clinical trials investigating this further.

The focus of this scientific statement is on novel therapies to mitigate the effects of post-cardiac arrest brain injury. While the search for effective treatments continues and whether identified in the future, the value of post-cardiac arrest rehabilitation must not be forgotten. The reader is referred to further information on survivorship and rehabilitation, which is given in detail elsewhere.<sup>119,120</sup>

In summary, the reasons for failure to translate preclinical animal data into clinical results are multifactorial. The complexity of ischemic brain injury and the accrued and limited understanding of the neuroprotective mechanisms at the current time make achieving a step change challenging. If we are to find success in future work, these barriers must be systematically addressed in future trials. Odds of successful translation of interventions from animals to humans might be improved when preclinical data address the population (works in multiple species, works with multiple severities of brain injury), the intervention (has a defined dose, has a defined therapeutic window), and the outcomes (improves final functional recovery specifically of the brain).

## FUTURE TRIAL DESIGNS

### A Family's Story

*On February 11, 2023, our son Michael, who was 26, suffered a cardiac arrest stemming from a lack of oxygen in his body shortly after admission to the hospital. The intensive care unit team at Vancouver General Hospital were able to restart his heart, but there were concerns of permanent brain injury due to the prolonged period during which his brain did not receive adequate oxygen. Unfortunately, Michael's MRI and related examinations revealed significant brain injury, which would not render him to regain consciousness and live the quality of life that he desired.*

*When given this news, our family was devastated as we worked with the health care professionals to come to accept that we would lose our son. On February 21, 2023, Michael passed away peacefully with our family by his side. Michael was a giving, generous, and kind person. He was full of life and always sought to help others. He was and will always be our inspiration.*

*It is our hope that by sharing Michael's story and our family's loss, researchers and health care professionals will appreciate the devastating nature of this disease entity for families and coalesce together around common approaches, ideas, and study designs to improve patients' chances at full recovery. We greatly appreciate the opportunity to share our son's story and wish the medical community our best in understanding this disease and improving outcomes for patients, families, and loved ones.*

*Lora Peeler and David Boloten (parents)*

The past decade has seen significant progress through multicenter collaboration,<sup>84,85</sup> designs that have enabled evaluation of >1 intervention at a time,<sup>49,110,121</sup> evolution<sup>122</sup> and standardization of end points,<sup>9,10</sup> and protocolizing prognostication and decisions for early withdrawal of life-sustaining treatments,<sup>85</sup> with concurrent overall improvement in quality.<sup>123</sup> The remainder of this section considers how future trial designs can build on these gains.

### Scope of the Problem

RCTs remain the most robust way to evaluate the efficacy and effectiveness of an intervention or therapy. Aside from the general challenges of securing funding and designing and achieving sufficient recruitment rates, there are challenges that are specific to cardiac arrest RCTs. The clinical complexity and heterogeneity seen in cardiac arrest necessitate recruitment of sufficient patients to adequately discern differences in response across phenotypes, often calling for large numbers across multiple centers. Post-cardiac arrest brain injury goes through multiple stages, each with diverse and concurrent pathophysiological pathways (Table 1 and Figure 1). Accordingly, the interventions delivered have specific therapeutic windows and should correspond to the presence (timing) and duration of the targeted pathophysiology. This concept is underrecog-

nized and therefore results in a mismatch between interventions and the phase(s) of post-cardiac arrest brain injury in which the interventions are meant to intervene. Practical issues may influence the feasibility of timing of delivery, particularly in the prehospital setting.

Interventions typically go through an exploratory phase II RCT and a confirmatory phase III RCT in evaluating efficacy. Ideally, phase II cardiac arrest RCTs should be designed to determine whether an intended intervention can affect the mechanistic pathway. The outcome measures should be mechanistic and adequately reflect the engagement of the target mechanism. Clinical and patient-centered outcomes may be included as secondary outcomes. Investigators should avoid the temptation for a phase II trial becoming an underpowered phase III trial. Phase III RCTs should be designed and powered to examine patient-centered outcomes (eg, survival, neurological outcome, and health-related quality of life) and ideally measure mechanisms and postintervention confounders believed to mediate these outcomes (Figure 2).

Throughout health care, there is a recognition that different disease phenotypes may respond differently to interventions. In the context of critical care, this has been demonstrated in sepsis,<sup>124</sup> COVID-19,<sup>125</sup> and acute respiratory distress syndrome.<sup>126,127</sup> Although this may also prove to be the case for resuscitated cardiac arrest patients, the a priori subgroup analyses from the individual patient meta-analysis of the TTM-1 and TTM-2 found consistent effects in all predefined subgroups, with no single phenotype showing a benefit of either temperature strategy.<sup>128</sup> Accelerating progress in cardiac arrest care will require new strategies and corresponding advances in trial methodology, with a focus on optimal patient population (sample size and phenotype), leveraging of novel trial designs, and strategic selection of biomarkers according to the mechanism of intervention and phase of trials.

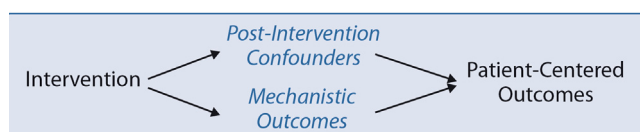
### Optimization of Study Design (Which Trial)

Most prior randomized trials in cardiac arrest used the traditional fixed, parallel-group RCT designs testing 1 intervention at a time.<sup>85,93,129</sup> A new trial was built each time a new intervention was studied, which was time and resource intensive. Newer trial designs relevant to post-cardiac arrest brain injury include umbrella and adaptive trials.<sup>130</sup> Umbrella trials test targeted treatments in specific (often biomarker-defined) subgroups (Figure 3). At its most general, an adaptive clinical trial uses data accruing within the trial

#### Phase II Trials



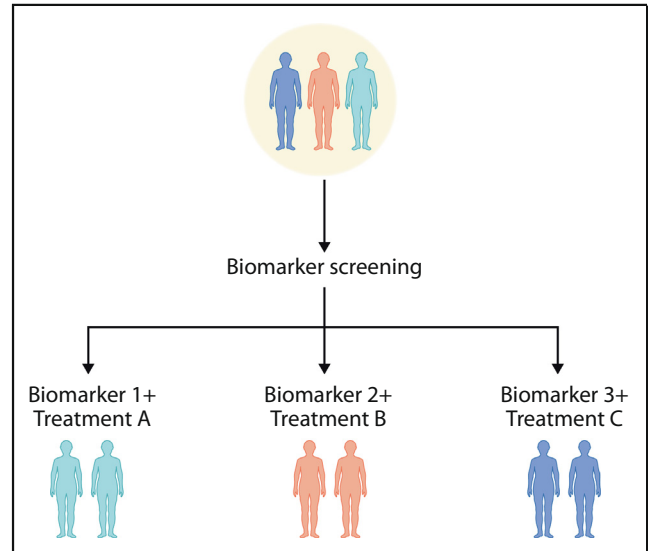
#### Phase III Trials



#### Pragmatic Phase III Trial



**Figure 2 – Patient-centered outcomes in phase II and phase III trials.**



**Figure 3 – Umbrella trial. Umbrella trials recruit patients with a single underlying condition such as cardiac arrest. Multiple treatments are tested in specific (often biomarker-defined) subgroups. The differences in color of the human figures represent the heterogeneity of patient phenotypes.**

to make decisions about whether to continue the trial and where to allocate remaining patients.<sup>131</sup> Platform trials are an emerging subtype of adaptive designs that enable multiple therapies to be evaluated efficiently (Figure 4).<sup>132</sup> Previously used successfully in oncology, adaptive platform trials gained interest during the COVID-19 pandemic because they provided evidence rapidly to guide clinical practice.<sup>133,134</sup>

Adopting a similar strategy in cardiac arrest may be operationally and statistically more efficient in the following ways:

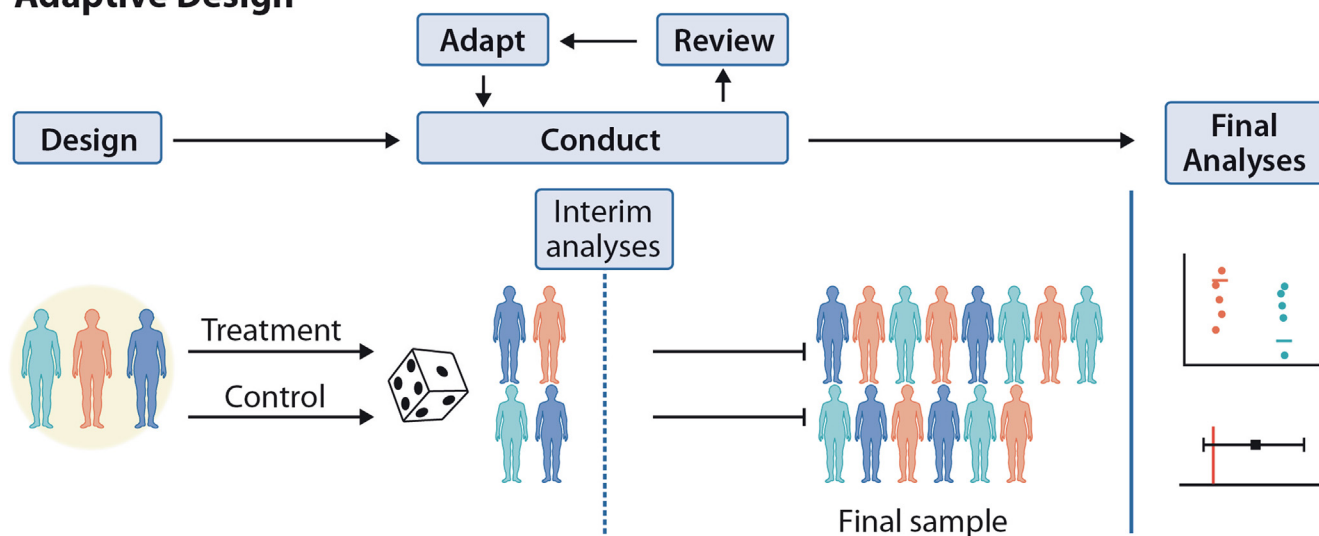
1. With the master protocol as a foundation, multiple interventions may be concurrently compared with a common control arm, or the same patient could be randomized to different treatments at different phases of their illness (Figure 5).<sup>135</sup>
2. Key features of the trial design (enrollment criteria, sample size, randomization, interventions, analysis) could be modified in response to accumulating results from trial participants.
3. Adaptive platform trials enable a pipeline of phase II studies.
4. Adaptive platform trials could also facilitate seamless transition from phase II to phase III studies.

Similarly, moving from the more traditional frequentist analysis, which is underpinned by a dichotomous interpretation of trial findings based on a P value, to a Bayesian trial analysis may provide a more nuanced interpretation of trial findings and may support better decisions about our understanding of the efficacy and effectiveness of interventions.<sup>128</sup>

### Optimization of Population (Whom to Include)

Patients with cardiac arrest are extremely heterogeneous. This includes variation in the cause of the cardiac arrest, the patient

## Adaptive Design



**Potential changes:** Target sample size, treatment arms/doses, allocation ratios, enrollment criteria

**Adaptive trial:** A multistage study that uses accumulating trial data in scheduled interim analyses to make prespecified changes to the trial's course while maintaining validity and integrity of the trial

**Figure 4 - Adaptive design.** In an adaptive trial design, the trial protocol includes scheduled, interim looks at the accumulating data (review phase). In the adapt phase, a priori-defined modifications can be executed on the basis of the findings of the interim analyses. Examples of adaptations include refining the sample size, changing the allocation of patients to trial arms, abandoning treatments or doses, and stopping the trial. Because adaptations are defined in advance, the trial validity and integrity are preserved.

demographics (and underlying physiology or pathophysiology), and the treatment that patients receive. This heterogeneity necessitates recruiting large sample sizes into RCTs to reliably detect differences between groups. This challenge may drive trialists to target unrealistic treatment effects in sample size calculations.

Enrichment of the trial population provides an opportunity to target patient groups most likely to benefit from an intervention. To date, this enrichment has often been based on cardiac arrest characteristics. For example, the TTM-2 trial included only patients who were unable to obey verbal commands and excluded patients who had an unwitnessed asystolic cardiac arrest.<sup>85</sup> These criteria were driven by the need to exclude patient groups who were seemingly too well or too unwell to derive any likely benefit from the intervention. When such decisions are made, a balance needs to be struck between focusing on the populations most likely to benefit and the limitations that such selection has on generalizability.

There are 2 key limitations to this approach. First, excluding key important patient groups means that the effectiveness of the intervention in these patient groups will remain unclear. Second, this type of enrichment may not best identify the patient groups most likely to benefit from the intervention. One solution to the second limitation is to develop an enriched trial population, using biomarkers to identify those most likely to benefit from the intervention according to its known mechanism of action. Such an approach is exemplified by the recent TELSTAR trial (Treatment of Electroencephalographic Status Epilepticus After Cardiopulmonary Resuscitation), in which patients were enrolled only if they had periodic or rhythmic activity based on electroencephalographic monitoring.<sup>136</sup> Potential biomark-

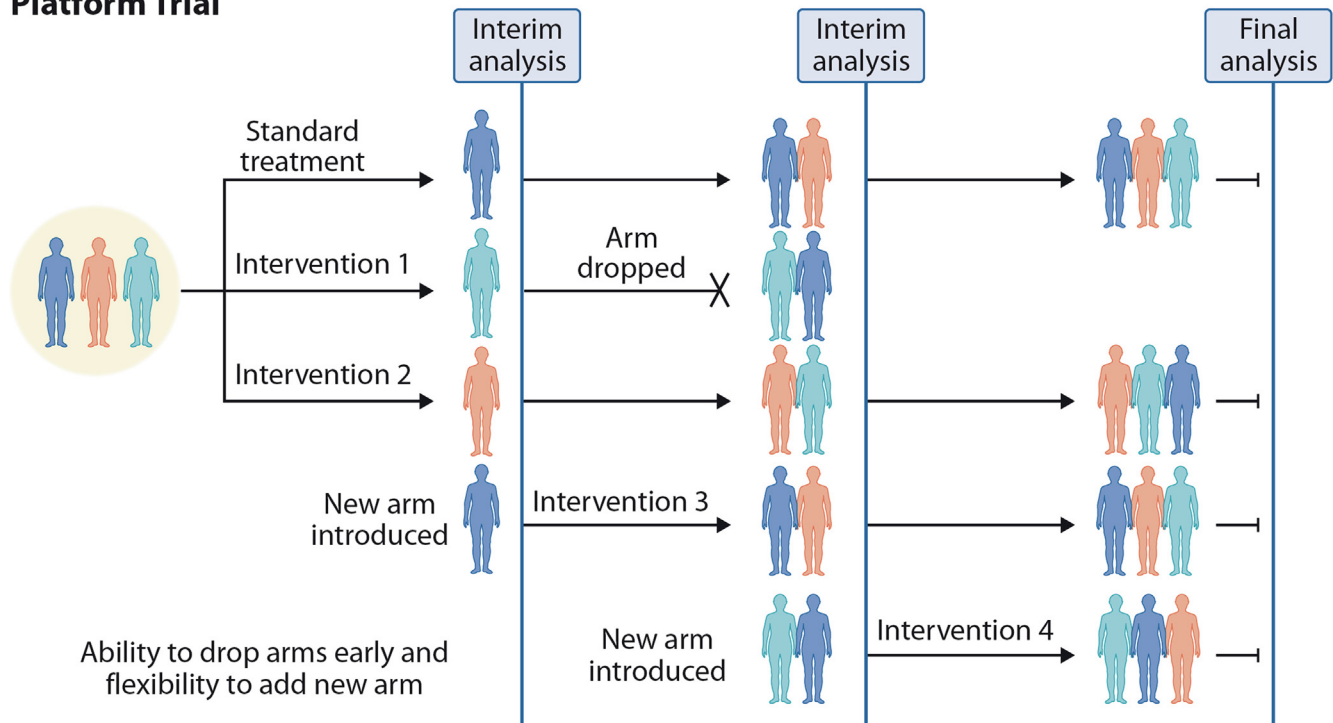
ers may include blood, imaging, or patient physiology (Supplemental Table 5). However, we lack good biomarkers to predict the development of brain injury at admission. Furthermore, the time-critical nature of intervention delivery after cardiac arrest means that any biomarker that has a predictable correlation with mechanistic engagement and injury severity must be available before delivery of the intervention.

### Optimization of Intervention

The time-critical and complex pathophysiology of cardiac arrest brain injury means that individual interventions, particularly when they focus on a single target, are unlikely to produce a meaningful and detectable effect. The evaluation of multiple interventions (with multiple or different mechanistic targets), particularly those that work synergistically, and titration of interventions according to effect are more likely to produce a detectable difference in outcome. For example, in the context of HIV infection, inhibiting viral replication with a single agent was not effective, but the introduction of combination therapies targeting multiple mechanisms drastically improved survival.<sup>137</sup> One challenge in this approach is that trial findings may not inform our understanding of the relative contribution of specific interventions to the overall effect.

The target population for most post-cardiac arrest brain injury trials will be patients with signs of neurological impairment such as confusion or unresponsiveness. There may be specific challenges in rapidly administering drugs or implementing interventions to prevent or treat cardiac arrest brain injury in this patient group such as competing priorities in relation to patient stabilization, consent

## Platform Trial



**Figure 5 – Platform trial. Basic outline for a cardiac arrest platform trial. Domains include putative mechanisms of potential therapies, known as factors in the nomenclature of platform trials. Multiple factors in each domain can be tested; comparisons with a standard treatment are also commonly used in this methodology. A regimen is a combination of specific factors applied to an individual. Not all individuals will be eligible for a treatment from each domain. Future mechanisms and therapies can be accommodated in the statistical framework. The differences in color of the human figures reflect the heterogeneity of patient phenotypes.**

procedures, access to research teams, and nonavailability of drug administration routes.

Deciding on the therapies to include in a platform is a complex; although a platform trial enables the comparison of multiple treatments, the community does not and should not choose a single treatment to test at a time. The prioritization must be done with care by gathering input from multiple stakeholders, including but not limited to patients and their families, translational scientists, clinical researchers, clinicians, those funding or commissioning services, research funders, industry, and regulators. Last, a flexible or platform trial will have the ability to accommodate multiple therapies in different domains (mechanisms or therapy types).

### Optimization of Outcome Measures

#### Phase II Trials

The primary end point in a phase II trial should provide sufficient information about efficacy to support, when appropriate, the rapid progression to a phase III clinical trial. This might be a clinical outcome or a biomarker outcome (blood, imaging, physiological; [Supplemental Table 6](#)). The ideal outcome for a phase II trial would include the following:

1. Mapping to the mechanism of the treatment being evaluated;
2. Correlating with the clinical outcome that is likely to be chosen for a phase III trial (eg, survival, functional outcome);
3. Not revealing the treatment allocation in a blinded trial;

4. Being feasible to collect in participating study centers;
5. Being repeatable; and
6. Having readily available results.

The time point for collecting the primary end point should aim to coincide with the time at which the trial intervention is anticipated to have maximal effect. Trialists should ensure that trials collect key safety outcomes, particularly in the context of novel drugs or when the mechanism of action of the intervention may affect other organs.

Trial platforms may facilitate the seamless transition from a phase II to a phase III evaluation, provided that relevant progression criteria are met. In these cases, there will be a need to include phase III clinical effectiveness outcomes for the duration of the trial to ensure that data from all patients can be analyzed. Once progression criteria are met, it may be reasonable to drop mechanistic biomarkers if they are complex or costly to continue measuring. An ideal biomarker that maps to a treatment mechanism, correlates with clinical outcome, or both, does not currently exist. Appropriate statistical models can enable a platform to either simultaneously or sequentially address phase II and phase III questions and accommodate future treatment questions that are not known at the time of platform inception.

#### Phase III Trials

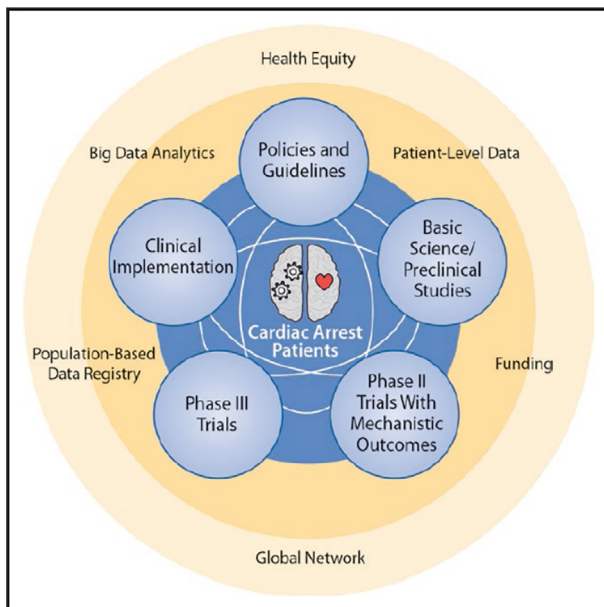
When a phase III trial is designed, the primary end point should be important to clinicians, patients, the public, and policymakers. Appro-

appropriate choice of the primary outcome will either accelerate implementation into clinical practice if the trial is positive or facilitate rapid deoption if the trial is neutral or shows harm. Alongside the importance of the primary outcome to stakeholders, key considerations in choosing a primary clinical outcome will include feasibility of measurement, completeness of data collection, and the plausibility of detecting a clinically important difference.

The Core Outcome Set for Cardiac Arrest framework identifies 3 core outcomes that should be reported in all cardiac arrest clinical trials: survival, functional outcome, and health-related quality of life.<sup>9,10</sup> In the context of post-cardiac arrest brain injury, it may be appropriate to explore the relevance of other core outcome sets such as those for stroke,<sup>138</sup> mechanical ventilation,<sup>139</sup> or traumatic brain injury.<sup>140</sup> There is currently no cardiac arrest-specific patient-reported outcome measure, but a new tool is currently being developed.<sup>141</sup>

### Conceptual Future State

Platform trials are one strategy to address several of the barriers currently facing the field. Such trials allow the inclusion of multiple treatments compared simultaneously with a control group, with the ability to add and remove treatment arms over the course of the trial. Recent examples include the REMAP-CAP trial (Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia)<sup>134</sup> and the ISPY-2 trial (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2) in breast cancer.<sup>133</sup> ISPY-2 evaluates drug treatment regimens in appropriate breast cancer phenotypes based on molecular tumor features such as estrogen receptor status. It is a phase II trial, with the output of the trial being a treatment that advances to definite testing against standard care when identified to have sufficient promise in a specific phenotype. A similar approach could be applied to cardiac arrest (Figure 6).



**Figure 6 – Translational platform to advance neuroprotective therapies after cardiac arrest.**

## PRIORITIZATION OF BARRIERS TO THE DISCOVERY AND TRANSLATION OF NEUROPROTECTIVE THERAPIES FOR POST-CARDIAC ARREST BRAIN INJURY

### Modified Delphi Methods

At a hybrid (in-person and virtual) writing group meeting in December 2022, the authors identified and prioritized key barriers to the discovery and translation of neuroprotective therapies after cardiac arrest. Writing group members were asked in an open-ended question to identify their top 3 barriers to improving the neurological outcome of patients with cardiac arrest. An anonymous, electronic web-based voting platform (Qualtrics, Provo, UT) was used. Responses were collated and synthesized by themes.

The writing group discussed and refined the responses into 6 thematic barriers: (1) understanding of post-cardiac arrest brain injury mechanisms; (2) characterization of patient heterogeneity; (3) development of biomarkers; (4) delivery of the therapy at the right time and dose after cardiac arrest; (5) complexity of study design; and (6) translational research infrastructure. The subthemes of these barriers are further outlined in Supplemental Table 7. The identified barriers in the understanding of post-cardiac arrest brain injury mechanisms, characterization of patient heterogeneity, and lack of biomarkers are discussed in detail in the prior sections. Therefore, the following sections focus on the remaining barriers: delivery of therapy, complexity of study design, and translational research infrastructure. Figure 6 illustrates the proposed integrative approach that can transform the translational infrastructure to advance neuroprotective therapies after cardiac arrest.

### Delivery of the Therapy to the Right Patients at the Right Time and Dose

Significant challenges exist among preclinical study design, clinical trial inception and execution, and clinical implementation. A therapy that targets the initial minutes after cardiac arrest during ischemic depolarization and reperfusion repolarization would have to be implemented in the prehospital setting by lay rescuers or emergency medical service professionals. Such therapy should ideally be easy to deliver, have a forgiving safety profile, and be stable in varied environments. In contrast, a therapy that targets dysregulation could be implemented in the prehospital settings, emergency departments, or intensive care units, depending on its optimal therapeutic window, route of administration, dosing regimen, and patient phenotypes.

### Complexity of Study Design

#### Small Effect Size

Cardiac arrest clinical trials have been limited by insufficient sample size to evaluate the efficacy of therapies with small effect size. For example, the total number of patients with cardiac arrest from RCTs that have evaluated the effect of hypothermia is <3000 to date.<sup>123</sup> Therefore, available evidence does not rule out an absolute effect size of 2% to 3%, which may well be in line with a realistic effect size for critical care trials. This would translate into a number needed to treat of 30 to 50, which may be justifiable to most patients, clinicians, and families. A 2-arm RCT with equal allocation and 90% power at a 2-sided  $\alpha$  level of 0.05 that could detect an intervention that improved survival from 10% to 12% would require a total sample size of 10

256, assuming no loss to follow-up. As a comparison, a systematic review of the use of thrombolytic therapy for acute myocardial infarction was able to meta-analyze data from >40 000 patients who had been included in randomized trials.<sup>142</sup> It is likely that therapies such as opening of blocked arteries for myocardial infarction may not be sufficient for the complex cellular cascades that occur after post-cardiac arrest reperfusion. Larger trials aiming for more realistic effect sizes will require international collaboration to enroll patients from many sites.

### **Multimodal Therapy**

The complexity of post-cardiac arrest brain injury suggests that monotherapies are unlikely to be as successful as polydrug and multimodal neuroprotective therapies. After the failure of multiple monotherapies, polytherapies have become the mainstream for the treatment of complex diseases such as cancer and HIV. The success of preclinical treatment of severe brain injury has been demonstrated with multimodal therapeutic approaches. Recent data revealed that a multimodal approach comprising an extracorporeal pulsatile-perfusion system and a hemoglobin-based, acellular, non-coagulative, and cytoprotective perfusate can restore multiple functions to swine brains after an extended period of total ischemia, a feat not previously thought to be possible.<sup>39</sup>

The development of polydrug and multimodal therapies for post-cardiac arrest brain injury faces several barriers attributable to the complex metabolic dysregulation observed in this disease state. The brain has multiple geographic brain regions, cell types, and time windows of vulnerability and activation after ischemia, which require a customized therapeutic approach. Knowledge of the relative importance of different mechanisms is incomplete. The design of clinical trials is also challenging because of the different pathophysiology of cardiac arrest at different phases, thereby requiring substantial methodological work. Clinical trials must test not only multiple treatments at a single time but also multiple treatments given sequentially according to responses to earlier treatments. End points must be tailored to each regimen or mechanism rather than comparing dissimilar treatments on the same scale. Many registered phase II trials in cardiac arrest lack a primary end point focused on mechanistic proof of concept (Supplemental Table 6), which could be detrimental to the discovery of novel neuroprotective therapies after cardiac arrest.

### **Translational Research Infrastructure**

#### *Multidisciplinary Collaboration*

To advance the discovery and translation of neuroprotective therapies for patients with cardiac arrest, the barriers between different research disciplines and geographic locations must be removed. This can be achieved through fostering collaboration and communication between researchers and stakeholders, including those in emergency medical services, emergency medicine, critical care, and rehabilitation. Designing a large-scale learning trial that involves hundreds of sites in multiple countries and disciplines may benefit from engaging organizations such as the International Liaison Committee on Resuscitation and its councils across the globe. They can provide guidance in evidence evaluation for study designs and facilitate international networks. Patient and stakeholder engagement is crucial throughout study development to ensure that patient-centered outcomes are prioritized. It is also important to advocate for equitable and ethical clinical trial conduct through policies and scientific guidelines at the regional, national, and international levels. Breaking down translational silos and promoting collaboration can

accelerate the discovery and translation of neuroprotective therapies for patients with cardiac arrest, ultimately improving their outcomes.

### **Enrollment and Consent**

One challenge in designing trials is ensuring that research processes do not introduce delays in intervention delivery. Data from the CRASH RCT (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; corticosteroids in head injury) and CRASH-2 RCT (tranexamic acid in major trauma) show how delays in treatment delivery resulting from trial processes can influence the observed treatment effect.<sup>143,144</sup> For this reason, trials of post-cardiac arrest brain injury, whenever ethically and legally permissible, should seek to use deferred consent or exception from informed consent to minimize these delays.

Randomization processes may also introduce delays. Although cluster randomization may facilitate rapid randomization, potential advantages may be offset by the need for larger sample sizes, potential loss of allocation concealment, inability to stratify randomization, and low treatment adherence. For example, in the AIRWAYS-2 cluster RCT (Airway Management in Out of Hospital Cardiac Arrest Patients) comparing advanced airway management strategies in out-of-hospital cardiac arrest, ~18% of participants did not receive any advanced airway.<sup>145</sup> Electronic systems that facilitate individual randomization with allocation concealment and facilitate stratification are extremely attractive, albeit potentially limited by cellular or internet connection issues in some settings. The development of novel electronic randomization can overcome the limitations of connectivity.<sup>146,147</sup>

### **Infrastructure**

The complexity of cardiac arrest clinical trials necessitates collaborative support from the scientific communities, cardiac arrest survivors and their families, funders, and policymakers. Overlaying big data analytics of existing electronic medical health records on population-based registries may be more efficient and affordable than attempting to establish independent trial data infrastructure for each study. Furthermore, machine-learning algorithms and federated databases may enable patient-, region-, and population-level data analyses.

### **Funding**

Creating the initial design and managing the adaptation to data as they are acquired would require a major investment of time and money. However, when built, such a trial would be flexible enough to incorporate the biomarkers and treatments of the future. It likely would even attract investment from the private sector, which has generally avoided cardiac arrest, given easier pathways in relatively less complex diseases on the mechanistic level. Alternative funding mechanisms are also needed to support high-risk, high-reward ideas to innovate and reimagine strategies with which we design, test, and translate promising neuroprotective therapies from the preclinical space to clinical trials.

## **CONCLUSIONS**

The mechanisms of post-cardiac arrest brain injury are complex and inadequately understood. From the available evidence, we propose a mechanistic construct that includes 4 sequential phases aligned with temporal stages of disease progression and treatment. The multiple, often overlapping, causal mechanisms and variations in an individ-

ual's response to injury and treatment make it unlikely that targeting a single mechanism with a one-size-fits-all approach in a heterogeneous patient population will result in a significant impact on patient outcomes.

In the ideal state, clinical trials should be preceded by high-quality mechanistic studies designed to enable therapies to be delivered that are based on the presence, timing, and duration of the targeted mechanism. Biomarkers of mechanistic target engagement should be developed to identify patients with the targeted mechanism of injury, to quantify its severity, and to measure the response to therapy. These biomarkers should be developed and validated in preclinical models along with the associated therapy and then used in subsequent clinical trials to monitor mechanistic target engagement.

A new approach is needed that compares treatment effects of multicomponent, biologically informed, sequential regimens in specific groups of patients. In this future state, the field could discover

groundbreaking treatments within targeted phenotypes and focus on expanding the number of phenotypes with effective treatment strategies.

## ARTICLE INFORMATION

The American Heart Association, the European Resuscitation Council, and the International Liaison Committee on Resuscitation make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

## Disclosures

### Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Gavin D. Perkins	Warwick Medical School, University of Warwick (United Kingdom)	Resuscitation Council UK†	None	None	None	None	None	None
Robert Neumar	University of Michigan	American Heart Association†; Laerdal Foundation†	None	None	None	None	None	None
Anders Åneman	Liverpool Hospital, Sydney (Australia)	MRFF (The Medical Research Future Fund)†	None	None	None	None	None	None
Lance B. Becker	Donald & Barbara Zucker School of Medicine	Nihon Kohden*; United Therapeutics*	None	None	None	Cyotprotective IP*	NIH†	None
Clifton W. Callaway	University of Pittsburgh	NIH†	None	None	None	Patents related to ECG analysis during cardiac arrest or during chest pain; not licensed and no royalties*	None	None
Keith Couper	Warwick Medical School, University of Warwick (United Kingdom)	None	None	None	None	None	None	None
Karen G. Hirsch	Stanford University	NIH†	None	None	None	None	None	None
Cornelia W.E. Hoedemaekers	Radboud UMC (Netherlands)	None	None	None	None	None	None	None
Cindy H. Hsu	University of Michigan	None	None	None	None	None	None	None



<b>(continued)</b>								
Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Shir Lynn Lim	National University Heart Center	National University Health System Seed Grant†; Zoll Foundation†; National Medical Research Council Singapore Transitional Award†	None	None	None	None	None	None
William Meurer	University of Michigan	None	None	None	None	None	None	None
Jerry P. Nolan	Warwick Medical School, University of Warwick (United Kingdom)	None	None	None	None	None	None	None
Theresa Olasveengen	Oslo University Hospital and University of Oslo (Norway)	None	None	None	None	None	Laerdal Foundation*	None
Mypinder S. Sekhon	University British Columbia (Canada)	None	None	None	None	None	None	None
Markus Skrifvars	Helsinki University Hospital and University of Helsinki (Finland)	None	None	BARD Medical*	None	None	None	None
Jasmeet Soar	Southmead Hospital (United Kingdom)	None	None	None	None	None	None	None
Min-Shan Tsai	National Taiwan University Hospital and National Taiwan University College of Medicine (Taiwan)	None	None	None	None	None	None	None
Bhuma Vengamma	Resuscitation Council of India (India)	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Giuseppe Citerio	University of Milan-Bicocca (Italy)	None	None	None	None	None	None	None
Tobias Cronberg	Lund University (Sweden)	None	None	None	None	None	None	None
Hans Friberg	Skane University Hospital (Sweden)	None	None	None	None	None	None	None
Joshua R. Lupton	Oregon Health and Science University	Society for Academic Emergency Medicine† (research training grant related to cardiac arrest); Zoll Foundation† (completed grant related to cardiac arrest care)	None	None	None	None	None	None
Damon C. Scales	Sunnybrook Health Sciences Centre (Canada)	CIHR* (operating grant within past 2 years to study cardiac arrest treatments)	None	None	None	None	None	None
Jose I. Suarez	Johns Hopkins University	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

\*Modest.

†Significant.

## Acknowledgments

The authors are grateful for the support and approval of this scientific statement by the International Liaison Committee on Resuscitation and its member councils at the time of the drafting of this statement (American Heart Association, Australia and New Zealand Resuscitation Council, European Resuscitation Council, Heart and Stroke Foundation Canada, Inter-American Heart Foundation, Resuscitation Council of Asia, and Resuscitation Council of Southern Africa). The authors acknowledge the support of Amber Hoover in coordinating the writing of this statement. The authors thank our patient and family contributors Asad Kayani, David and Lora Peeler, and Carmen Choi for sharing their stories and inspiring us to do more to improve the outcomes of our patients. The illustrations were produced by Helen Schmidt. This scientific statement was funded by a grant from the Resuscitation Council UK.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resuscitation.2024.110196>.

## REFERENCES

- Grasner JT, Herlitz J, Tjelmeland IBM, Wnent J, Masterson S, Lilja G, Bein B, Bottiger BW, Rosell-Ortiz F, Nolan JP, et al. European Resuscitation Council guidelines 2021: epidemiology of cardiac arrest in Europe. *Resuscitation* 2021;161:61–79. <https://doi.org/10.1016/j.resuscitation.2021.02.007>.
- Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association [published correction appears in *Circulation*. 2022;146:e141]. *Circulation* 2022;145:e153–639. <https://doi.org/10.1161/CIR.0000000000001052>.
- Kiguchi T, Okubo M, Nishiyama C, Maconochie I, Ong MEH, Kern KB, Wyckoff MH, McNally B, Christensen EF, Tjelmeland I, et al. Out-of-hospital cardiac arrest across the world: first report from the International Liaison Committee on Resuscitation (ILCOR). *Resuscitation* 2020;152:39–49. <https://doi.org/10.1016/j.resuscitation.2020.02.044>.
- Nishiyama C, Kiguchi T, Okubo M, Alihodzic H, Al-Araji R, Baldi E, Beganton F, Booth S, Bray J, Christensen E, et al. Three-year trends in out-of-hospital cardiac arrest across the world: second report from the International Liaison Committee on Resuscitation (ILCOR). *Resuscitation* 2023;186. <https://doi.org/10.1016/j.resuscitation.2023.109757> 109757.

5. Grasner JT, Whent J, Herlitz J, Perkins GD, Lefering R, Tjelmeland I, Koster RW, Masterson S, Rossell-Ortiz F, Maurer H, et al. Survival after out-of-hospital cardiac arrest in Europe: results of the EuReCa TWO study. *Resuscitation* 2020;148:218–26. <https://doi.org/10.1016/j.resuscitation.2019.12.042>.
6. Beck B, Bray J, Cameron P, Smith K, Walker T, Grantham H, Hein C, Thorrowgood M, Smith A, Inoue M, et al. Regional variation in the characteristics, incidence and outcomes of out-of-hospital cardiac arrest in Australia and New Zealand: results from the Aus-ROC Epistry. *Resuscitation* 2018;126:49–57. <https://doi.org/10.1016/j.resuscitation.2018.02.029>.
7. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, Ko PC, Leong BS, Khunkhlay N, Naroo GY, et al. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation* 2015;96:100–8. <https://doi.org/10.1016/j.resuscitation.2015.07.026>.
8. Perkins GD, Callaway CW, Haywood K, Neumar RW, Lilja G, Rowland MJ, Sawyer KN, Skrifvars MB, Nolan JP. Brain injury after cardiac arrest. *Lancet* 2021;398:1269–78. [https://doi.org/10.1016/S0140-6736\(21\)00953-3](https://doi.org/10.1016/S0140-6736(21)00953-3).
9. Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Bottiger BW, Brooks A, Castren M, Ong ME, Hazinski MF, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. *Circulation* 2018;137:e783–801. <https://doi.org/10.1161/CIR.0000000000000562>.
10. Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Bottiger BW, Brooks A, Castren M, Ong MEH, Hazinski MF, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. *Resuscitation* 2018;127:147–63. <https://doi.org/10.1016/j.resuscitation.2018.03.022>.
11. Doan TN, Rashford S, Pincus J, Bosley E. Cost-effectiveness of extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: a modelling study. *Resusc Plus* 2022;12. <https://doi.org/10.1016/j.resplu.2022.100309> 100309.
12. Achana F, Petrou S, Madan J, Khan K, Ji C, Hossain A, Lall R, Slowther AM, Deakin CD, Quinn T, et al. Cost-effectiveness of adrenaline for out-of-hospital cardiac arrest. *Crit Care* 2020;24:579. <https://doi.org/10.1186/s13054-020-03271-0>.
13. Efendijev I, Folger D, Raj R, Reinikainen M, Pekkarinen PT, Litonius E, Skrifvars MB. Outcomes and healthcare-associated costs one year after intensive care-treated cardiac arrest. *Resuscitation* 2018;131:128–34. <https://doi.org/10.1016/j.resuscitation.2018.06.028>.
14. Greif R, Bhanji F, Bigham BL, Bray J, Breckwoldt J, Cheng A, Duff JP, Gilfoyle E, Hsieh MJ, Iwami T, et al. Education, implementation, and teams: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Resuscitation* 2020;156:A188–239. <https://doi.org/10.1016/j.resuscitation.2020.09.014>.
15. Greif R, Bhanji F, Bigham BL, Bray J, Breckwoldt J, Cheng A, Duff JP, Gilfoyle E, Hsieh MJ, Iwami T, et al. Education, implementation, and teams: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2020;142:S222–83. <https://doi.org/10.1161/CIR.0000000000000896>.
16. Olasveengen TM, Mancini ME, Perkins GD, Avis S, Brooks S, Castren M, Chung SP, Considine J, Couper K, Escalante R, et al. Adult basic life support: International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Resuscitation* 2020;156:A35–79. <https://doi.org/10.1016/j.resuscitation.2020.09.010>.
17. Olasveengen TM, Mancini ME, Perkins GD, Avis S, Brooks S, Castren M, Chung SP, Considine J, Couper K, Escalante R, et al. Adult basic life support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2020;142:S41–91. <https://doi.org/10.1161/CIR.0000000000000892>.
18. Soar J, Berg KM, Andersen LW, Bottiger BW, Cacciola S, Callaway CW, Couper K, Cronberg T, D'Arrigo S, Deakin CD, et al. Adult advanced life support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation* 2020;156:A80–A119. <https://doi.org/10.1016/j.resuscitation.2020.09.012>.
19. Berg KM, Soar J, Andersen LW, Bottiger BW, Cacciola S, Callaway CW, Couper K, Cronberg T, D'Arrigo S, Deakin CD, et al. Adult advanced life support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2020;142:S92–S139. <https://doi.org/10.1161/CIR.0000000000000893>.
20. Sandroni C, Cronberg T, Sekhon M. Brain injury after cardiac arrest: pathophysiology, treatment, and prognosis. *Intensive Care Med* 2021;47:1393–414. <https://doi.org/10.1007/s00134-021-06548-2>.
21. Andersen LW, Lind PC, Vammen L, Hoybye M, Holmberg MJ, Granfeldt A. Adult post-cardiac arrest interventions: an overview of randomized clinical trials. *Resuscitation* 2020;147:1–11. <https://doi.org/10.1016/j.resuscitation.2019.12.003>.
22. Perkins GD, Neumar R, Monsieurs KG, Lim SH, Castren M, Nolan JP, Nadkarni V, Montgomery B, Steen P, Cummins R, et al. The International Liaison Committee on Resuscitation: review of the last 25 years and vision for the future. *Resuscitation* 2017;121:104–16. <https://doi.org/10.1016/j.resuscitation.2017.09.029>.
23. Pulsinelli WA. Selective neuronal vulnerability: morphological and molecular characteristics. *Prog Brain Res* 1985;63:29–37. [https://doi.org/10.1016/S0079-6123\(08\)61973-1](https://doi.org/10.1016/S0079-6123(08)61973-1).
24. Bjorklund E, Lindberg E, Rundgren M, Cronberg T, Friberg H, Englund E. Ischaemic brain damage after cardiac arrest and induced hypothermia: a systematic description of selective eosinophilic neuronal death: a neuropathologic study of 23 patients. *Resuscitation* 2014;85:527–32. <https://doi.org/10.1016/j.resuscitation.2013.11.022>.
25. Daniele SG, Trummer G, Hossmann KA, Vrselja Z, Benk C, Gobeske KT, Damjanovic D, Andrijevic D, Pooth JS, Dellal D, et al. Brain vulnerability and viability after ischaemia. *Nat Rev Neurosci* 2021;22:553–72. <https://doi.org/10.1038/s41583-021-00488-y>.
26. Ton HT, Raffensperger K, Shoykhet M. Early thalamic injury after resuscitation from severe asphyxial cardiac arrest in developing rats. *Front Cell Dev Biol* 2021;9. <https://doi.org/10.3389/fcell.2021.737319> 737319.
27. Neumar RW. Molecular mechanisms of ischemic neuronal injury. *Ann Emerg Med* 2000;36:483–506. <https://doi.org/10.1067/mem.2000.110995>.
28. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat Med* 2011;17:439–47. <https://doi.org/10.1038/nm.2333>.
29. Shibasaki F, Hallin U, Uchino H. Calcineurin as a multifunctional regulator. *J Biochem* 2002;131:1–15. <https://doi.org/10.1093/oxfordjournals.jbchem.a003063>.
30. Bevers MB, Neumar RW. Mechanistic role of calpains in postischemic neurodegeneration. *J Cereb Blood Flow Metab* 2008;28:655–73. <https://doi.org/10.1038/sj.cbfm.9600595>.
31. Erecinska M, Silver IA. Calcium handling by hippocampal neurons under physiologic and pathologic conditions. *Adv Neurol* 1996;71:119–36.
32. Muralikrishna Adibhatla R, Hatcher JF. Phospholipase A2, reactive oxygen species, and lipid peroxidation in cerebral ischemia. *Free Radic Biol Med* 2006;40:376–87. <https://doi.org/10.1016/j.freeradbiomed.2005.08.044>.
33. Du T, Mestre H, Kress BT, Liu G, Sweeney AM, Samson AJ, Rasmussen MK, Mortensen KN, Bork PAR, Peng W, et al. Cerebrospinal fluid is a significant fluid source for anoxic cerebral

- oedema. *Brain* 2022;145:787–97. <https://doi.org/10.1093/brain/awab293>.
34. Mizoue R, Takeda Y, Sato S, Takata K, Morimatsu H. Cerebral blood flow threshold is higher for membrane repolarization than for depolarization and is lowered by intraschemic hypothermia in rats. *Crit Care Med* 2015;43:e350–5. <https://doi.org/10.1097/CCM.0000000000001095>.
  35. Symon L. Flow thresholds in brain ischaemia and the effects of drugs. *Br J Anaesth* 1985;57:34–43. <https://doi.org/10.1093/bja/57.1.34>.
  36. Dreier JP, Major S, Foreman B, Winkler MKL, Kang EJ, Milakara D, Lemale CL, DiNapoli V, Hinzman JM, Woitzik J, et al. Terminal spreading depolarization and electrical silence in death of human cerebral cortex. *Ann Neurol* 2018;83:295–310. <https://doi.org/10.1002/ana.25147>.
  37. Leao AA. Further observations on the spreading depression of activity in the cerebral cortex. *J Neurophysiol* 1947;10:409–14. <https://doi.org/10.1152/in.1947.10.6.409>.
  38. Andrijevic D, Vrselja Z, Lysyy T, Zhang S, Skarica M, Spajic A, Dellal D, Thorn SL, Duckrow RB, Ma S, et al. Cellular recovery after prolonged warm ischaemia of the whole body. *Nature* 2022;608:405–12. <https://doi.org/10.1038/s41586-022-05016-1>.
  39. Vrselja Z, Daniele SG, Silbereis J, Talpo F, Morozov YM, Sousa AMM, Tanaka BS, Skarica M, Pletikos M, Kaur N, et al. Restoration of brain circulation and cellular functions hours post-mortem. *Nature* 2019;568:336–43. <https://doi.org/10.1038/s41586-019-1099-1>.
  40. Alevriadou BR, Patel A, Noble M, Ghosh S, Gohil VM, Stathopoulos PB, Madesh M. Molecular nature and physiological role of the mitochondrial calcium uniporter channel. *Am J Physiol Cell Physiol* 2021;320:C465–82. <https://doi.org/10.1152/ajpcell.00502.2020>.
  41. Bonora M, Giorgi C, Pinton P. Molecular mechanisms and consequences of mitochondrial permeability transition. *Nat Rev Mol Cell Biol* 2022;23:266–85. <https://doi.org/10.1038/s41580-021-00433-y>.
  42. Bottiger BW, Krumnikl JJ, Gass P, Schmitz B, Motsch J, Martin E. The cerebral “no-reflow” phenomenon after cardiac arrest in rats: influence of low-flow reperfusion. *Resuscitation* 1997;34:79–87. [https://doi.org/10.1016/s0300-9572\(96\)01029-5](https://doi.org/10.1016/s0300-9572(96)01029-5).
  43. Fischer M, Hossmann KA. No-reflow after cardiac arrest. *Intensive Care Med* 1995;21:132–41. <https://doi.org/10.1007/BF01726536>.
  44. Leonov Y, Sterz F, Safar P, Johnson DW, Tisherman SA, Oku K. Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs. *Stroke* 1992;23:45–53. <https://doi.org/10.1161/01.str.23.1.45>.
  45. Cao W, Carney JM, Duchon A, Floyd RA, Chevion M. Oxygen free radical involvement in ischemia and reperfusion injury to brain. *Neurosci Lett* 1988;88:233–8. [https://doi.org/10.1016/0304-3940\(88\)90132-2](https://doi.org/10.1016/0304-3940(88)90132-2).
  46. Dux E, Mies G, Hossmann KA, Siklos L. Calcium in the mitochondria following brief ischemia of gerbil brain. *Neurosci Lett* 1987;78:295–300. [https://doi.org/10.1016/0304-3940\(87\)90376-4](https://doi.org/10.1016/0304-3940(87)90376-4).
  47. Muoio V, Persson PB, Sendeski MM. The neurovascular unit: concept review. *Acta Physiol (Oxf)* 2014;210:790–8. <https://doi.org/10.1111/apha.12250>.
  48. Hoiland RL, Ainslie PN, Wellington CL, Cooper J, Stukas S, Thiara S, Foster D, Fergusson NA, Conway EM, Menon DK, et al. Brain hypoxia is associated with neuroglial injury in humans post-cardiac arrest. *Circ Res* 2021;129:583–97. <https://doi.org/10.1161/CIRCRESAHA.121.319157>.
  49. Kjaergaard J, Moller JE, Schmidt H, Grand J, Molstrom S, Borregaard B, Venø S, Sarkisian L, Mamaev D, Jensen LO, et al. Blood-pressure targets in comatose survivors of cardiac arrest. *N Engl J Med* 2022;387:1456–66. <https://doi.org/10.1056/NEJMoa2208687>.
  50. Ameloot K, De Deyne C, Eertmans W, Ferdinande B, Dupont M, Palmers PJ, Petit T, Nuyens P, Maeremans J, Vundelinckx J, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. *Eur Heart J* 2019;40:1804–14. <https://doi.org/10.1093/eurheartj/ehz120>.
  51. Jakkula P, Reinikainen M, Hastbacka J, Loisa P, Tiainen M, Pettila V, Toppila J, Lahde M, Backlund M, Okkonen M, et al. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Med* 2018;44:2112–21. <https://doi.org/10.1007/s00134-018-5453-9>.
  52. Hoedemaekers CW, Ainslie PN, Hinssen S, Aries MJ, Bisschops LL, Hofmeijer J, van der Hoeven JG. Low cerebral blood flow after cardiac arrest is not associated with anaerobic cerebral metabolism. *Resuscitation* 2017;120:45–50. <https://doi.org/10.1016/j.resuscitation.2017.08.218>.
  53. Mauracher LM, Buchtele N, Schorghofer C, Weiser C, Herkner H, Merrelaar A, Spiel AO, Hell L, Ay C, Pabinger I, et al. Increased citrullinated histone H3 Levels in the early post-resuscitative period are associated with poor neurologic function in cardiac arrest survivors: a prospective observational study. *J Clin Med* 2019;8:1568. <https://doi.org/10.3390/jcm8101568>.
  54. Bowness JM. Cartilage fucoproteins with sites for cross-linking by transglutaminase. *Biochem Cell Biol* 1987;65:280–5. <https://doi.org/10.1139/o87-036>.
  55. Lemiale V, Huet O, Vigue B, Mathonnet A, Spaulding C, Mira JP, Carli P, Duranteau J, Cariou A. Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. *Resuscitation* 2008;76:17–24. <https://doi.org/10.1016/j.resuscitation.2007.06.028>.
  56. Wolfson Jr SK, Safar P, Reich H, Clark JM, Gur D, Stezoski W, Cook EE, Krupper MA. Dynamic heterogeneity of cerebral hypoperfusion after prolonged cardiac arrest in dogs measured by the stable xenon/CT technique: a preliminary study. *Resuscitation* 1992;23:1–20. [https://doi.org/10.1016/0300-9572\(92\)90158-9](https://doi.org/10.1016/0300-9572(92)90158-9).
  57. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a “two-hit” model. *Crit Care* 2017;21:90. <https://doi.org/10.1186/s13054-017-1670-9>.
  58. Kirschen MP, Majmudar T, Diaz-Arastia R, Berg R, Abella BS, Topjian A, Balu R. Deviations from PRx-derived optimal blood pressure are associated with mortality after cardiac arrest. *Resuscitation* 2022;175:81–7. <https://doi.org/10.1016/j.resuscitation.2022.03.003>.
  59. Sekhon MS, Gooderham P, Menon DK, Brasher PMA, Foster D, Cardim D, Czosnyka M, Smielewski P, Gupta AK, Ainslie PN, et al. The burden of brain hypoxia and optimal mean arterial pressure in patients with hypoxic ischemic brain injury after cardiac arrest. *Crit Care Med* 2019;47:960–9. <https://doi.org/10.1097/CCM.0000000000003745>.
  60. Laurikkala J, Aneman A, Peng A, Reinikainen M, Pham P, Jakkula P, Hastbacka J, Wilkman E, Loisa P, Toppila J, et al. Association of deranged cerebrovascular reactivity with brain injury following cardiac arrest: a post-hoc analysis of the COMACARE trial. *Crit Care* 2021;25:350. <https://doi.org/10.1186/s13054-021-03764-6>.
  61. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 1993;34:S37–53. <https://doi.org/10.1111/j.1528-1157.1993.tb05905.x>.
  62. Andersen JV, Schousboe A. Milestone review: metabolic dynamics of glutamate and GABA mediated neurotransmission: the essential roles of astrocytes. *J Neurochem* 2023;166:109–1373. <https://doi.org/10.1111/jnc.15811>.
  63. Guo C, Ma YY. Calcium permeable-AMPA receptors and excitotoxicity in neurological disorders. *Front Neural Circuits* 2021;15. <https://doi.org/10.3389/fncir.2021.711564>.
  64. Verma M, Lizama BN, Chu CT. Excitotoxicity, calcium and mitochondria: a triad in synaptic neurodegeneration. *Transl Neurodegener* 2022;11:3. <https://doi.org/10.1186/s40035-021-00278-7>.

65. Datta S, Jaiswal M. Mitochondrial calcium at the synapse. *Mitochondrion* 2021;59:135–53. <https://doi.org/10.1016/j.mito.2021.04.006>.
66. Wang M, Pan W, Xu Y, Zhang J, Wan J, Jiang H. Microglia-mediated neuroinflammation: a potential target for the treatment of cardiovascular diseases. *J Inflamm Res* 2022;15:3083–94. <https://doi.org/10.2147/JIR.S350109>.
67. Chang Y, Zhu J, Wang D, Li H, He Y, Liu K, Wang X, Peng Y, Pan S, Huang K. NLRP3 inflammasome-mediated microglial pyroptosis is critically involved in the development of post-cardiac arrest brain injury. *J Neuroinflammation* 2020;17:219. <https://doi.org/10.1186/s12974-020-01879-1>.
68. Cirillo C, Brihmat N, Castel-Lacanal E, Le Fric A, Barbieux-Guillot M, Raposo N, Pariante J, Viguier A, Simonetta-Moreau M, Albuher JF, et al. Post-stroke remodeling processes in animal models and humans. *J Cereb Blood Flow Metab* 2020;40:3–22. <https://doi.org/10.1177/0271678X19882788>.
69. Alia C, Spalletti C, Lai S, Panarese A, Lamola G, Bertolucci F, Vallone F, Di Garbo A, Chisari C, Micera S, et al. Neuroplastic changes following brain ischemia and their contribution to stroke recovery: novel approaches in neurorehabilitation. *Front Cell Neurosci* 2017;11:76. <https://doi.org/10.3389/fncel.2017.00076>.
70. Farokhi-Sisakht F, Farhoudi M, Sadigh-Eteghad S, Mahmoudi J, Mohaddes G. Cognitive rehabilitation improves ischemic stroke-induced cognitive impairment: role of growth factors. *J Stroke Cerebrovasc Dis* 2019;28. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.07.015> 104299.
71. Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, Kawahara N, Tamura A, Kirino T, Nakafuku M. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 2002;110:429–41. [https://doi.org/10.1016/s0092-8674\(02\)00862-0](https://doi.org/10.1016/s0092-8674(02)00862-0).
72. Ohira K, Furuta T, Hioki H, Nakamura KC, Kuramoto E, Tanaka Y, Funatsu N, Shimizu K, Oishi T, Hayashi M, et al. Ischemia-induced neurogenesis of neocortical layer 1 progenitor cells. *Nat Neurosci* 2010;13:173–9. <https://doi.org/10.1038/nn.2473>.
73. Jurkowski MP, Bettio L, Woo EK, Patten A, Yau S-Y, Gil-Mohapel J. Beyond the hippocampus and the SVZ: adult neurogenesis throughout the brain. *Front Cell Neurosci* 2020;14. <https://doi.org/10.3389/fncel.2020.576444> 576444.
74. Chen P, Chen F, Wu Y, Zhou B. New insights into the role of aberrant hippocampal neurogenesis in epilepsy. *Front Neurol* 2021;12. <https://doi.org/10.3389/fneur.2021.727065> 727065.
75. Safar P, Abramson NS, Angelos M, Cantadore R, Leonov Y, Levine R, Pretto E, Reich H, Sterz F, Stezoski SW, et al. Emergency cardiopulmonary bypass for resuscitation from prolonged cardiac arrest. *Am J Emerg Med* 1990;8:55–67. [https://doi.org/10.1016/0735-6757\(90\)90298-e](https://doi.org/10.1016/0735-6757(90)90298-e).
76. Statler KD, Alexander H, Vagni V, Holubkov R, Dixon CE, Clark RS, Jenkins L, Kochanek PM. Isoflurane exerts neuroprotective actions at or near the time of severe traumatic brain injury. *Brain Res* 2006;1076:216–24. <https://doi.org/10.1016/j.brainres.2005.12.106>.
77. Statler KD, Alexander H, Vagni V, Dixon CE, Clark RS, Jenkins L, Kochanek PM. Comparison of seven anesthetic agents on outcome after experimental traumatic brain injury in adult, male rats. *J Neurotrauma* 2006;23:97–108. <https://doi.org/10.1089/neu.2006.23.97>.
78. Bleyaert AL, Nemoto EM, Safar P, Stezoski SM, Mickell JJ, Moossy J, Rao GR. Thiopental amelioration of brain damage after global ischemia in monkeys. *Anesthesiology* 1978;49:390–8. <https://doi.org/10.1097/0000542-197812000-00003>.
79. Nagel S, Papadakis M, Hoyte L, Buchan AM. Therapeutic hypothermia in experimental models of focal and global cerebral ischemia and intracerebral hemorrhage. *Expert Rev Neurother* 2008;8:1255–68. <https://doi.org/10.1586/14737175.8.8.1255>.
80. Traystman RJ. Animal models of focal and global cerebral ischemia. *ILAR J* 2003;44:85–95. <https://doi.org/10.1093/ilar.44.2.85>.
81. Lind PC, Johannsen CM, Vammen L, Magnussen A, Andersen LW, Granfeldt A. Translation from animal studies of novel pharmacological therapies to clinical trials in cardiac arrest: a systematic review. *Resuscitation* 2021;158:258–69. <https://doi.org/10.1016/j.resuscitation.2020.10.028>.
82. Fabian-Jessing BK, Vallentin MF, Secher N, Hansen FB, Dezfulian C, Granfeldt A, Andersen LW. Animal models of cardiac arrest: a systematic review of bias and reporting. *Resuscitation* 2018;125:16–21. <https://doi.org/10.1016/j.resuscitation.2018.01.047>.
83. Vognsen M, Fabian-Jessing BK, Secher N, Lofgren B, Dezfulian C, Andersen LW, Granfeldt A. Contemporary animal models of cardiac arrest: a systematic review. *Resuscitation* 2017;113:115–23. <https://doi.org/10.1016/j.resuscitation.2017.01.024>.
84. Eastwood G, Nichol AD, Hodgson C, Parke RL, McGuinness S, Nielsen N, Bernard S, Skrifvars MB, Stub D, Taccone FS, et al. Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest. *N Engl J Med* 2023. <https://doi.org/10.1056/NEJMoa2214552>.
85. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullen S, Rylander C, Wise MP, Oddo M, Cariou A, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med* 2021;384:2283–94. <https://doi.org/10.1056/NEJMoa2100591>.
86. Xu K, Puchowicz MA, Sun X, LaManna JC. Decreased brainstem function following cardiac arrest and resuscitation in aged rat. *Brain Res* 2010;1328:181–9. <https://doi.org/10.1016/j.brainres.2010.02.080>.
87. Xu K, LaManna JC. The loss of hypoxic ventilatory responses following resuscitation after cardiac arrest in rats is associated with failure of long-term survival. *Brain Res* 2009;1258:59–64. <https://doi.org/10.1016/j.brainres.2008.12.059>.
88. Capone A, Safar P, Radovsky A, Wang YF, Peitzman A, Tisherman SA. Complete recovery after normothermic hemorrhagic shock and profound hypothermic circulatory arrest of 60 minutes in dogs. *J Trauma* 1996;40:388–95. <https://doi.org/10.1097/00005373-199603000-00011>.
89. Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med*. 1986;314:397–403. <https://doi.org/10.1056/NEJM198602133140701>.
90. Arrich J, Herkner H, Mullner D, Behringer W. Targeted temperature management after cardiac arrest: a systematic review and meta-analysis of animal studies. *Resuscitation* 2021;162:47–55. <https://doi.org/10.1016/j.resuscitation.2021.02.002>.
91. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556. <https://doi.org/10.1056/NEJMoa012689>.
92. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63. <https://doi.org/10.1056/NEJMoa003289>.
93. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med* 2013;369:2197–206. <https://doi.org/10.1056/NEJMoa1310519>.
94. Le May M, Osborne C, Russo J, So D, Chong AY, Dick A, Froeschl M, Glover C, Hibbert B, Marquis JF, et al. Effect of moderate vs mild therapeutic hypothermia on mortality and neurologic outcomes in comatose survivors of out-of-hospital cardiac arrest: the CAPITAL CHILL randomized clinical trial. *JAMA* 2021;326:1494–503. <https://doi.org/10.1001/jama.2021.15703>.
95. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, Coupez E, Dequin PF, Cariou A, Boulain T, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. *N Engl J Med* 2019;381:2327–37. <https://doi.org/10.1056/NEJMoa1906661>.

96. Wolfrum S, Roedel K, Hanebutte A, Pfeifer R, Kurowski V, Riessen R, Daubmann A, Braune S, Soffker G, Bibiza-Freiwald E, et al. Temperature control after in-hospital cardiac arrest: a randomized clinical trial. *Circulation* 2022;146:1357–66. <https://doi.org/10.1161/CIRCULATIONAHA.122.060106>.
97. Aneman A, Frost S, Parr M, Skrifvars MB. Target temperature management following cardiac arrest: a systematic review and Bayesian meta-analysis. *Crit Care* 2022;26:58. <https://doi.org/10.1186/s13054-022-03935-z>.
98. Hazelton JL, Balan I, Elmer GI, Kristian T, Rosenthal RE, Krause G, Sanderson TH, Fiskum G. Hyperoxic reperfusion after global cerebral ischemia promotes inflammation and long-term hippocampal neuronal death. *J Neurotrauma* 2010;27:753–62. <https://doi.org/10.1089/neu.2009.1186>.
99. Okuma Y, Becker LB, Hayashida K, Aoki T, Saeki K, Nishikimi M, Shoaib M, Miyara SJ, Yin T, Shinozaki K. Effects of post-resuscitation normoxic therapy on oxygen-sensitive oxidative stress in a rat model of cardiac arrest. *J Am Heart Assoc* 2021;10. <https://doi.org/10.1161/JAHA.120.018773> e018773.
100. Alva R, Mirza M, Baiton A, Lazuran L, Samokys L, Bobinski A, Cowan C, Jaimon A, Obioru D, Al Makhoul T, et al. Oxygen toxicity: cellular mechanisms in normobaric hyperoxia. *Cell Biol Toxicol* 2023;39:111–43. <https://doi.org/10.1007/s10565-022-09773-7>.
101. Johnston AJ, Steiner LA, Gupta AK, Menon DK. Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity. *Br J Anaesth* 2003;90:774–86. <https://doi.org/10.1093/bja/aeg104>.
102. Pilcher J, Weatherall M, Shirlcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest: a systematic review and meta-analysis of animal trials. *Resuscitation* 2012;83:417–22. <https://doi.org/10.1016/j.resuscitation.2011.12.021>.
103. Thomas A, van Diepen S, Beekman R, Sinha SS, Brusca SB, Alviar CL, Jentzer J, Bohula EA, Katz JN, Shah A, et al. Oxygen supplementation and hyperoxia in critically ill cardiac patients: from pathophysiology to clinical practice. *JACC Adv* 2022;1. <https://doi.org/10.1016/j.jacadv.2022.100065> 100065.
104. Palmer E, Post B, Klappaugh R, Marra G, MacCallum NS, Brealey D, Ercole A, Jones A, Ashworth S, Watkinson P, et al. The association between suprathreshold arterial oxygen levels and mortality in critically ill patients: a multicenter observational cohort study. *Am J Respir Crit Care Med* 2019;200:1373–80. <https://doi.org/10.1164/rccm.201904-0849OC>.
105. Martin J, Mazer-Amirshahi M, Pourmand A. The impact of hyperoxia in the critically ill patient: a review of the literature. *Respir Care* 2020;65:1202–10. <https://doi.org/10.4187/respcare.07310>.
106. Hochberg CH, Semler MW, Brower RG. Oxygen toxicity in critically ill adults. *Am J Respir Crit Care Med* 2021;204:632–41. <https://doi.org/10.1164/rccm.202102-0417CI>.
107. Kuisma M, Boyd J, Voipio V, Alaspaa A, Roine RO, Rosenberg P. Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. *Resuscitation* 2006;69:199–206. <https://doi.org/10.1016/j.resuscitation.2005.08.010>.
108. Young P, Bailey M, Bellomo R, Bernard S, Dicker B, Freebairn R, Henderson S, Mackle D, McArthur C, McGuinness S, et al. HyperOxic Therapy OR NormOxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): a randomised controlled feasibility trial. *Resuscitation* 2014;85:1686–91. <https://doi.org/10.1016/j.resuscitation.2014.09.011>.
109. Bray JE, Hein C, Smith K, Stephenson M, Grantham H, Finn J, Stub D, Cameron P, Bernard S, Investigators EXACT. Oxygen titration after resuscitation from out-of-hospital cardiac arrest: a multi-centre, randomised controlled pilot study (the EXACT pilot trial). *Resuscitation* 2018;128:211–5. <https://doi.org/10.1016/j.resuscitation.2018.04.019>.
110. Schmidt H, Kjaergaard J, Hassager C, Molstrom S, Grand J, Borregaard B, Roelsgaard Obling LE, Veno S, Sarkisian L, Mamaev D, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med* 2022;387:1467–76. <https://doi.org/10.1056/NEJMoa2208686>.
111. Bernard SA, Bray JE, Smith K, Stephenson M, Finn J, Grantham H, Hein C, Masters S, Stub D, Perkins GD, et al. Effect of lower vs higher oxygen saturation targets on survival to hospital discharge among patients resuscitated after out-of-hospital cardiac arrest: the EXACT randomized clinical trial. *JAMA* 2022;328:1818–26. <https://doi.org/10.1001/jama.2022.17701>.
112. Young P, Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, Finfer S, Freebairn R, King V, et al. Conservative oxygen therapy for mechanically ventilated adults with suspected hypoxic ischaemic encephalopathy. *Intensive Care Med* 2020;46:2411–22. <https://doi.org/10.1007/s00134-020-06196-y>.
113. Schjorring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, Backlund M, Keus F, Laake JH, Morgan M, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med* 2021;384:1301–11. <https://doi.org/10.1056/NEJMoa2032510>.
114. Helmerhorst HJ, Arts DL, Schultz MJ, van der Voort PH, Abu-Hanna A, de Jonge E, van Westerloo DJ. Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med* 2017;45:187–95. <https://doi.org/10.1097/CCM.0000000000002084>.
115. Liang M, Ahmad F, Dickinson R. Neuroprotection by the noble gases argon and xenon as treatments for acquired brain injury: a preclinical systematic review and meta-analysis. *Br J Anaesth* 2022;129:200–18. <https://doi.org/10.1016/j.bja.2022.04.016>.
116. Banks P, Franks NP, Dickinson R. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor mediates xenon neuroprotection against hypoxia-ischemia. *Anesthesiology* 2010;112:614–22. <https://doi.org/10.1097/ALN.0b013e3181cea398>.
117. Arola OJ, Laitio RM, Roine RO, Gronlund J, Saraste A, Pietila M, Airaksinen J, Perttila J, Scheinin H, Olkkola KT, et al. Feasibility and cardiac safety of inhaled xenon in combination with therapeutic hypothermia following out-of-hospital cardiac arrest. *Crit Care Med* 2013;41:2116–24. <https://doi.org/10.1097/CCM.0b013e31828a4337>.
118. Laitio R, Hynninen M, Arola O, Virtanen S, Parkkola R, Saunavaara J, Roine RO, Gronlund J, Ylikoski E, Wennervirta J, et al. Effect of inhaled xenon on cerebral white matter damage in comatose survivors of out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2016;315:1120–8. <https://doi.org/10.1001/jama.2016.1933>.
119. Sawyer KN, Camp-Rogers TR, Kotini-Shah P, Del Rios M, Gossip MR, Moitra VK, Haywood KL, Dougherty CM, Lubitz SA, Rabinstein AA, et al. on behalf of the American Heart Association Emergency Cardiovascular Care Committee; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; Council on Quality of Care and Outcomes Research; and Stroke Council. Sudden cardiac arrest survivorship: a scientific statement from the American Heart Association. *Circulation* 2020;141:e654–85. <https://doi.org/10.1161/CIR.0000000000000747>.
120. Nolan JP, Sandroni C, Bottiger BW, Cariou A, Cronberg T, Friberg H, Genbrugge C, Haywood K, Lilja G, Moulart VRM, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Resuscitation* 2021;161:220–69. <https://doi.org/10.1016/j.resuscitation.2021.02.012>.
121. Hassager C, Schmidt H, Moller JE, Grand J, Molstrom S, Beske RP, Boesgaard S, Borregaard B, Bekker-Jensen D, Dahl JS, et al. Duration of device-based fever prevention after cardiac arrest. *N Engl J Med* 2023;388:888–97. <https://doi.org/10.1056/NEJMoa2212528>.
122. Haywood KL, Pearson N, Morrison LJ, Castren M, Lilja G, Perkins GD. Assessing health-related quality of life (HRQoL) in survivors of out-of-hospital cardiac arrest: a systematic review of patient-

- reported outcome measures. *Resuscitation* 2018;123:22–37. <https://doi.org/10.1016/j.resuscitation.2017.11.065>.
123. Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW. International Liaison Committee on Resuscitation Advanced Life Support Task Force. Targeted temperature management in adult cardiac arrest: systematic review and meta-analysis. *Resuscitation* 2021;167:160–72. <https://doi.org/10.1016/j.resuscitation.2021.08.040>.
124. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* 2019;321:2003–17. <https://doi.org/10.1001/jama.2019.5791>.
125. Goligher EC, Lawler PR, Jensen TP, Talisa V, Berry LR, Lorenzi E, McVerry BJ, Chang CH, Leifer E, Bradbury C, et al. Heterogeneous treatment effects of therapeutic-dose heparin in patients hospitalized for COVID-19. *JAMA* 2023;329:1066–77. <https://doi.org/10.1001/jama.2023.3651>.
126. McAuley DF, Laffey JG, O’Kane CM, Perkins GD, Mullan B, Trinder TJ, Johnston P, Hopkins PA, Johnston AJ, McDowell C, et al. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med* 2014;371:1695–703. <https://doi.org/10.1056/NEJMoa1403285>.
127. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, McDowell C, Laffey JG, O’Kane CM, McAuley DF. Irish Critical Care Trials Group. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018;6:691–8. [https://doi.org/10.1016/S2213-2600\(18\)30177-2](https://doi.org/10.1016/S2213-2600(18)30177-2).
128. Holgersson J, Meyer MAS, Dankiewicz J, Lijja G, Ullén S, Hassager C, Cronberg T, Wise MP, Bělohávek J, Hovdenes J, et al. Hypothermic versus normothermic temperature control after cardiac arrest. *NEJM Evidence* 2022;1. <https://doi.org/10.1056/EVIDoa2200137> EVIDoa2200137.
129. Kirkegaard H, Soreide E, de Haas I, Pettila V, Taccone FS, Arus U, Storm C, Hassager C, Nielsen JF, Sorensen CA, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2017;318:341–50. <https://doi.org/10.1001/jama.2017.8978>.
130. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med* 2017;377:62–70. <https://doi.org/10.1056/NEJMr1510062>.
131. Thorlund K, Haggstrom J, Park JJ, Mills EJ. Key design considerations for adaptive clinical trials: a primer for clinicians. *BMJ* 2018;360. <https://doi.org/10.1136/bmj.k698> k698.
132. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA* 2015;313:1619–20. <https://doi.org/10.1001/jama.2015.2316>.
133. Carey LA, Winer EP. I-SPY 2: toward more rapid progress in breast cancer treatment. *N Engl J Med* 2016;375:83–4. <https://doi.org/10.1056/NEJMe1603691>.
134. UPMC REMAP-COVID Group, on behalf of the REWMAP-CAP Investigators. Implementation of the Randomized Embedded Multifactorial Adaptive Platform for COVID-19 (REMAP-COVID) trial in a US health system: lessons learned and recommendations. *Trials*. 2021;22:100. <https://doi.org/10.1186/s13063-020-04997-6>.
135. Park JH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, Lester RT, Thorlund K, Mills EJ. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019;20:572. <https://doi.org/10.1186/s13063-019-3664-1>.
136. Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, Tromp SC, Scholten E, Horn J, van Rootselaar AF, Admiraal MM, et al. Treating rhythmic and periodic EEG patterns in comatose survivors of cardiac arrest. *N Engl J Med* 2022;386:724–34. <https://doi.org/10.1056/NEJMoa2115998>.
137. Porter K, Babiker A, Bhaskaran K, Darbyshire J, Pezzotti P, Porter K, Walker AS, Collaboration C. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *Lancet* 2003;362:1267–74. [https://doi.org/10.1016/S0140-6736\(03\)14570-9](https://doi.org/10.1016/S0140-6736(03)14570-9).
138. Salinas J, Sprinkhuizen SM, Ackerson T, Bernhardt J, Davie C, George MG, Gething S, Kelly AG, Lindsay P, Liu L, et al. An international standard set of patient-centered outcome measures after stroke. *Stroke* 2016;47:180–6. <https://doi.org/10.1161/STROKEAHA.115.010898>.
139. Blackwood B, Ringrow S, Clarke M, Marshall JC, Connolly B, Rose L, McAuley DF. A core outcome set for critical care ventilation trials. *Crit Care Med* 2019;47:1324–31. <https://doi.org/10.1097/CCM.0000000000003904>.
140. Wilde EA, Whiteneck GG, Bogner J, Bushnik T, Cifu DX, Dikmen S, French L, Giacino JT, Hart T, Malec JF, et al. Recommendations for the use of common outcome measures in traumatic brain injury research. *Arch Phys Med Rehabil* 2010;91:1650–1660.e17. <https://doi.org/10.1016/j.apmr.2010.06.033>.
141. Haywood KL, Southern C, Tutton E, Swindell P, Ellard D, Pearson NA, Parsons H, Couper K, Dainty KN, Agarwal S, et al. An international collaborative study to co-produce a patient-reported outcome measure of cardiac arrest survivorship and health-related quality of life (CASHQoL): a protocol for developing the long-form measure. *Resusc Plus* 2022;11. <https://doi.org/10.1016/j.resplu.2022.100288> 100288.
142. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992;327:248–54. <https://doi.org/10.1056/NEJM199207233270406>.
143. Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, Dewan Y, Gando S, Guyatt G, Hunt BJ, et al. CRASH-2 Collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011;377(1096–1101):1101.e1–2. [https://doi.org/10.1016/S0140-6736\(11\)60278-X](https://doi.org/10.1016/S0140-6736(11)60278-X).
144. Roberts I, Prieto-Merino D, Shakur H, Chalmers I, Nicholl J. Effect of consent rituals on mortality in emergency care research. *Lancet* 2011;377:1071–2. [https://doi.org/10.1016/S0140-6736\(11\)60317-6](https://doi.org/10.1016/S0140-6736(11)60317-6).
145. Bengier JR, Kirby K, Black S, Brett SJ, Clout M, Lazaroo MJ, Nolan JP, Reeves BC, Robinson M, Scott LJ, et al. Effect of a strategy of a supraglottic airway device vs tracheal intubation during out-of-hospital cardiac arrest on functional outcome: the AIRWAYS-2 randomized clinical trial. *JAMA* 2018;320:779–91. <https://doi.org/10.1001/jama.2018.11597>.
146. Bloom JE, Partovi A, Bernard S, Okyere D, Heritier S, Mahony E, Eliakundu AL, Dawson LP, Voskoboinik A, Anderson D, et al. Use of a novel smartphone-based application tool for enrolment and randomisation in pre-hospital clinical trials. *Resuscitation* 2023;187. <https://doi.org/10.1016/j.resuscitation.2023.109787> 109787.
147. Watkins S, Chowdhury FJ, Norman C, Brett SJ, Couper K, Goodwin L, Gould DW, Ae Harrison D, Hossain A, Lall R, et al. Randomised trial of the clinical and cost effectiveness of a supraglottic airway device compared with tracheal intubation for in-hospital cardiac arrest (AIRWAYS-3): Protocol, design and implementation. *Resusc Plus* 2023;15. <https://doi.org/10.1016/j.resplu.2023.100430> 100430.