Review

Wolf Creek XVII Part 8: Neuroprotection

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Abstract

Introduction: Post-cardiac arrest brain injury (PCABI) is the primary determinant of clinical outcomes for patients who achieve return of spontaneous circulation after cardiac arrest (CA). There are limited neuroprotective therapies available to mitigate the acute pathophysiology of PCABI.
Methods: Neuroprotection was one of six focus topics for the Wolf Creek XVII Conference held on June 14–17, 2023 in Ann Arbor, Michigan, USA. Conference invitees included international thought leaders and scientists in the field of CA resuscitation from academia and industry. Participants submitted via online survey knowledge gaps, barriers to translation, and research priorities for each focus topic. Expert panels used the survey results and their own perspectives and insights to create and present a preliminary unranked list for each category that was debated, revised and ranked by all attendees to identify the top 5 for each category.
Results: Top 5 knowledge gaps included developing therapies for neuroprotection; improving understanding of the pathophysiology, mechanisms, and natural history of PCABI; deploying precision medicine approaches; optimizing resuscitation and CPR quality; and determining optimal timing for and duration of interventions. Top 5 barriers to translation included patient heterogeneity; nihilism & lack of knowledge about cardiac arrest; challenges with the translational pipeline; absence of mechanistic biomarkers; and inaccurate neuro-triage and neuroprognostication. Top 5 research priorities focused on translational research and trial optimization; addressing patient heterogeneity and individualized interventions; improving understanding of pathophysiology and mechanisms; developing mechanistic and outcome biomarkers across post-CA time course; and improving implementation of science and technology.
Conclusion: This overview can serve as a guide to transform the care and outcome of patients with PCABI. Addressing these topics has the potential to improve both research and clinical care in the field of neuroprotection for PCABI.
Keywords: Cardiac arrest, Neuroprotection, Post-cardiac arrest brain injury

Introduction

Post-cardiac arrest brain injury (PCABI) is the primary determinant of clinical outcomes for patients who achieve return of spontaneous circulation (ROSC).[1,2] PCABI results from ischemia-reperfusion and the resultant injury to the cerebrum and related structures.[1,3–6] PCABI is associated with significant mortality, due to irreversible neurologic injury leading to death by neurologic criteria and/or withdrawal of life-sustaining therapy (WLST) for perceived poor neurologic prognosis.[7–9] In up to half of survivors, there is considerable morbidity due to long-term neuropsychiatric sequelae which impair functionality and quality of life.[10] Unfortunately, there are limited therapies available to mitigate the acute pathophysiology of PCABI and the downstream sequelae.[11,12]

The field of neuroprotection for PCABI is regrettably rife with interventions that showed promise in pre-clinical and early phase clinical studies but failed to translate into improved outcomes when tested in large randomized clinical trials.[13–16] The reasons for this discordance are likely numerous with heterogeneity in injury severity and care strategy, patient selection, trial design, and intervention-related factors at play.[17,18] Dissecting these reasons is key to developing an effective, integrative pipeline between pre-clinical, translational, and clinical research studies which may enhance the identification and validation of new neuroprotective strategies for PCABI.

Methods

Since its inception in 1975, the Wolf Creek Conference has a well-established tradition of providing a unique forum for robust intellectual exchange between thought leaders and scientists from academia and industry that focuses on advancing the science and practice of cardiac arrest resuscitation.[19] The Wolf Creek XVII Conference was hosted by the Max Harry Weil Institute for Critical Care Research and Innovation in Ann Arbor, Michigan, USA on

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June 15–17, 2023.[20] The 2023 conference focused on the "Future of Cardiac Arrest Resuscitation".

Neuroprotection was one of 6 focus topics for the Wolf Creek XVII Meeting. Meeting invitees included international academic and industry scientists as well as thought leaders in the field of cardiac arrest resuscitation. All participants were required to complete conflict of interest disclosures. Prior to the meeting, all participants were asked via online survey to list up to three knowledge gaps, barriers to translation and research priorities for each topic. Participants were instructed that the topic of neuroprotection would focus on therapeutic interventions initiated during CPR or after ROSC specifically targeting mechanism of brain injury caused by cardiac arrest.

Knowledge gaps were defined as areas where our understanding or knowledge is incomplete or limited. These gaps can arise due to various factors, such as lack of research, inadequate information, limited access to data or resources, or simply because the topic is new or complex. Barriers to translation were defined as obstacles that can prevent the successful transfer of knowledge or innovations from research or development settings to practical applications in the real world. Research priorities were defined as the areas of study that are considered most important or urgent by the scientific community or society as a whole. These priorities are often determined by a range of factors such as knowledge gaps, scientific breakthroughs, new challenges, societal needs or funding opportunities.

Panels made up of experts in each topic used the survey results and their own perspectives and insights to create an initial unranked list of up to ten items for each category. During the conference, expert panelists provided an overview of the current state and potential future state of the field lay the groundwork for an informed debate. This was followed by presentation and initial ranking of the knowledge gaps, barriers to translation, and research priorities by all attendees using electronic voting, discussion and revision by the panel and attendees, and then re-ranking. The top 5 items in each category underwent final review on the last day of the conference. An overview of the current and potential future state of the field and prioritized results for the topic of neuroprotection are presented and discussed in this manuscript. The complete results and rankings from all three categories are listed in Supplementary Materials.

Current state

The most effective neuroprotective strategy for patients with cardiac arrest is achieving ROSC as quickly as possible, and dissemination of the "chain of survival" concept led to improved outcomes after cardiac arrest.[21] Early recognition of cardiac arrest, activation of emergency medical services, high-quality CPR with minimized interruptions in chest compression, and timely defibrillation all play crucial roles in quickly achieving ROSC.[22] However, the goal of doubling survival rates after cardiac arrest by 2020 has not been achieved even after the wide dissemination and implementation of resuscitation guidelines,[23] and novel strategies are needed.

Current neuroprotective therapies applied after achieving ROSC are limited to supportive interventions to mitigate secondary brain injury.[11,24] This is mainly achieved by optimizing physiologic variables and treating causes of secondary brain injury such as seizures. Physiologic targets include brain and systemic oxygenation, carbon dioxide levels, brain and systemic perfusion, and temperature.[11] For example, optimization of cerebral oxygen delivery is a physiologically reasonable therapeutic intervention,[5] but clinical trials aiming to indirectly increase cerebral oxygen delivery through mean arterial pressure augmentation or mild hypercapnia have yielded neutral results.[15,25–27] Thus, additional promising therapeutic strategies are needed.

Hypothermic temperature control as a neuroprotective strategy has been used in mitigating PCABI.[28] In recent years, large multicenter randomized control trials have brought in to question many aspects of hypothermic temperature control after cardiac arrest, including strategies around optimal timing, duration, and target temperature, and additional trials are currently underway.[13,14,17] Current expert opinion recognizes that some populations of patients with PCABI might benefit from temperature control at temperatures between 33° and 36 °C,[8,11] though how to identify which patients may benefit and how to deliver the optimal duration and target temperature remains unknown.

Several pharmacologic neuroprotective agents that showed promising results in preclinical studies have been tested in clinical trials, but none has successfully translated to clinical practice.[29,30] Novel pharmacologic agents have recently shown promising results in early-stage clinical trials, and additional large-scale studies are eagerly anticipated.[31,32]

Current recommendations do not offer methods to tailor treatments for PCABI based on clinically relevant findings and injury severity. Methods to characterize injury severity have historically been limited to patient factors such as age, pre-arrest comorbidities, and baseline functional status, and resuscitation variables such as the durations of no- and low-flow time, whether the cardiac arrest was witnessed, initial cardiac rhythm, quality of resuscitation maneuvers provided, and the underlying cause of cardiac arrest.[1,2,33–35] As an example, an association between early inflammatory markers and metabolic changes, i.e. interleukin-6, procalcitonin, kynurenines, lactates, and PCABI has been studied, but not yet validated or used clinically to guide post-cardiac arrest care.[36–39] Individual pathophysiology,[40] genetic factors, and severity of brain injury have not routinely been evaluated and incorporated in to treatment decisions. This one-size-fits-all approach lacks refinement, and ideal post-cardiac arrest care strategies should identify individuals most likely to benefit from therapies and develop ways to target those therapies to individuals.

In addition to limitations in therapeutic interventions, current paradigms around neuroprognostication also have significant limitations. A multimodal prognostic approach with deferral of prognostication until at least 72 hours post-arrest when temperature returns to normothermia, confounding by sedatives and opioids is minimized, and post-arrest physiologic derangements clear is recommended.[11,41,42] However, most neuroprognostication research is considered to be of low certainty evidence and have significant risk of bias. Despite the recommendations for delaying prognostication, previous studies have shown that WLST occurs frequently within 72 hours after cardiac arrest. Among patients in whom WLST was selected, 16 % of them were predicted to have achieved functional recovery if WLST was not rendered.[43] Thus, the impacts of WLST and unreliable neuroprognostication are profound and impact both patient outcomes and also the development of therapies.[8]

Potential future state

An ideal future state will address opportunities in research and clinical care. From a pre-clinical research standpoint, and ideal future state should include improved rigor in the form of multiple sites and labs testing the same interventions akin to human trials; optimization of dose–response, pharmacokinetics and pharmacodynamics, and therapeutic time windows; testing between and across

species, sex, age, and comorbidities; using pre-clinical models that mimic clinical disease as closely as possible; and standardizing outcome assessments. To improve clinical studies, an ideal future state should focus on specific cardiac arrest sub-populations and target specific phenotypes and degrees of post-arrest injury. Developing early biomarkers or a panel of markers that would reliably reflect the severity of PCABI and predict its evolution in the short term and mortality and neurological outcomes in the long term would help shape treatment in each patient. Similarly, developing other biomarkers capable of monitoring the evolution of PCABI, i.e. neurofilament light chain or serial NSE measurements,[44–47] together with the neuro-imaging and monitoring, i.e. EEG, NIRS (near-infrared spectroscopy),[47] and other new technologies will aid real-time assessment of the patient response to a specific treatment and facilitate titration of dosage and duration, accordingly. This will also be helpful in identifying and including a predefined subgroup of patients who are amenable to benefit from a specific treatment in future clinical trials. Finally, it is also important that future clinical studies will address comprehensive functional and neuropsychiatric outcomes at longer time points post-arrest; account for differences in systems of care including across EMS interventions, post-arrest care, etc; and allow for robust trial networks to rapidly test multiple interventions.

Optimal research future states will also address current challenges related to funding, pipelines and pathways. From the standpoint of funding and pipeline development, innovation is somewhat necessarily limited by regulatory and safety constraints in medicine. The unfortunate impact of this is that the development of novel therapeutics takes many years and the process prevents the ability to "fail fast" and iterate quickly as seen in technology innovation in non-medical fields. Additionally, funding mechanisms limit high-risk studies and often stifle collaboration due to competition. An ideal future state would include a robust funding infrastructure to support cardiac arrest research with processes in place for rapid throughput of testing potentially promising interventions.

From a clinical standpoint, an ideal future state includes a focus on neuroprotective strategies across the spectrum of cardiac arrest care from the pre-hospital to critical care to recovery settings. Systems of care are deployed to allow for early administration of neuroprotective therapies, diversion of patients with out-of-hospital cardiac arrest to centers capable of delivering comprehensive neuroprotective post-arrest care, and seamless integration of multidisciplinary teams with expertise to care for these patients. Therapies are delivered and titrated to individuals based on need and responsiveness, ideally through real-time continuous evaluation of the patient's condition as well as response to treatment with sensible and specific essays. Neuroprognostication paradigms that address early triage and later neuroprognostication for long-term outcome are validated, sensitive, specific, and applied systematically.

Knowledge gaps

The current state of neuroprotection after cardiac arrest is limited by the failure to translate potentially promising therapeutics into clinical practice. The complexity of the PCABI pathophysiology and associated variability of the human brain injury spectrum represent significant challenges in identifying widely efficacious neuroprotective therapies for patients resuscitated from cardiac arrest.[1] The following top 5 knowledge gaps were identified and discussed by conference participants during the Neuroprotection Panel (Fig. 1).

1. Developing pharmacological therapies, combinations of therapies, and non-pharmacologic therapies for neuroprotection. A major knowledge gap is the absence of an effective scientific method of developing and translating new and effective therapies for neuroprotection. Indeed, the failure to translate any neuroprotective drug highlights the complex challenges in this field. Developing combination therapies with potentially complementary mechanisms of action, akin to human immunodeficiency virus therapies and some cancer therapies, may offer a synergistic impact. The current questions about temperature control to a hypothermic target highlight the importance of developing non-pharmacologic therapies that can be additive to potential pharmacologic therapies.

2. Improving understanding of the pathophysiology, mechanisms, and natural history of PCABI. The pathophysiology of cardiac arrest PCABI can be divided into different phases during the longitudinal arrest and post-arrest timeframes, and each of these phases has unique and dynamic pathophysiology. The phases of PCABI are the intra-arrest phase (during circulatory arrest with or without cardiopulmonary resuscitation), immediate post-resuscitation phase (reperfusion of the ischemic cerebral vasculature and brain tissue), and delayed dysregulation phase (occurring over hours and days). During each of the phases, perturbations in various physiologic and cellular pathways account for injury mechanisms that are attributed to the overall severity of PCABI and clinical outcomes. However, while various pathways involved in PCABI pathophysiology have been identified, key pathophysiologic knowledge gaps remain. As an example, the heterogeneity in the anatomic distribution of PCABI highlights the concept of 'selective vulnerability', which remains poorly understood mechanistically. Specific regions of the cerebrum are especially susceptible to PCABI including the grey matter, hippocampi, and deep nuclei. Improving understanding of this may lead to novel therapeutic targets, and unlocking fundamental research questions such as these may lead to key findings that can be leveraged to identify efficacious therapeutic strategies. The development of mechanistic biomarkers is also a critical knowledge gap. Studies have begun investigating the utility of different biomarkers not just as markers for poor outcomes, but to measure disease severity and to quantify treatment effects. Identifying novel and non-invasive biomarkers which reflect the pathophysiologic mechanisms at play in PCABI is required to determine if these mechanisms are in fact modifiable in humans.

3. Deploying precision medicine approaches: Identifying relevant characteristics of patient heterogeneity, determining which patients are most likely to benefit from different therapies, and targeting therapies to appropriate patients. The recognition of patient-specific pathophysiologic phenotypes has emerged in recent years. This notion refers to the concept of individual patients exhibiting signs of differential pathophysiologic mechanisms which may be upregulated or downregulated depending on the injury mechanism, severity, pattern, and other patient-specific factors. Intuitively, patients with different injury patterns and mechanisms may respond differently to different interventions. Identifying these patient phenotypes in a rapid and generalizable manner could lead to 'personalized resuscitation' approaches in the future.

4. Optimizing resuscitation and CPR quality with a focus on neuroprotection during resuscitation to improve long-term neurologic outcomes. Historically, the focus of CPR had been on achieving ROSC, but improvements in our understanding of cardiac arrest have led to a renewed focus on achieving neurologically intact survival. The acute, emergent, and time-limited features of cardiac arrest limit the ability to study the impact of acute resuscitation on neurologic parameters, especially in the out-of-hospital setting.

WOLF CREEK XVII | Neuroprotection - Top 5 Knowledge Gaps

1. Developing effective neuroprotective strategies and drugs to improve neurologic outcome; identifying correct time for delivery
2. Pathophysiology, natural history and time course of neurologic injury: understanding the mechanisms underlying neurologic injury
3. Identifying patients most likely to benefit from different therapies and targeting therapies appropriately: identifying heterogeneity and targeting phenotypes
4. Optimizing resuscitation and CPR quality: linking CPR quality to neurologic protection and outcome, improving quality of CPR
5. Determining optimal timing and duration of interventions

Fig. 1 – Neuroprotection: Top 5 knowledge gaps as ranked by attendees at Wolf Creek XVII, June 15–17, 2023, Ann Arbor, MI, USA.

Insights can be gleaned from case studies/series of hospitalized patients who have a cardiac arrest while undergoing invasive or non-invasive neuromonitoring for other indications. Non-invasive NIRS monitoring of the regional cerebral oxygen saturation during CPR are a potential tool for assessing the quality of the ongoing CPR.[48–50] NIRS and/or other similar real-time brain monitoring technologies may be helpful to assess the effectiveness of the resuscitation intervention and potentially giving feedback to immediate rescuers. Furthermore, the development of non-invasive measures that are easy to apply and provide continuous information during cardiac arrest will continue to improve our understanding of how acute resuscitation interventions impact neurologic parameters, and will ultimately improve interventions aimed at neurologic preservation during resuscitation.

5. Determining optimal timing for and duration of interventions. The timing of interventions targeting culprit mechanisms must be viewed in the context of the dynamic natural history of PCABI. Not doing so may lead to studies using interventions during time periods of PCABI pathophysiology for which the culprit mechanisms are not at play. Naturally, such studies would potentially lead to mistaken extrapolation of neutral results in clinical trials in regard to an intervention. A relevant example is the intervention of temperature control to a hypothermic target in comatose patients resuscitated from OHCA. Extended time is needed to reach the target temperature in human subjects compared to in animal studies, where cooling is usually rapidly achieved immediately after ROSC. Thus, it is possible that the target temperature in some human studies was only reached when the therapeutic window for this intervention had passed. In support of this hypothesis, there are numerous experimental animal studies suggesting that faster cooling can lead to a greater benefit after cardiac arrest.[51] In the TTM[13,14] and Hyperion[52] trials, the median time to reach the target temperature (33 °C) was approximately 8 hours after the ROSC. In contrast, intranasal cooling was proved to be able to allow for the rapid achievement of the target temperature (34 °C) compared to other methods,[53] and a sub-analysis of the Princess trial[54] showed a favorable trend after rapid intranasal cooling in the sub-population with a shockable presenting rhythm. Another example of possibly suboptimal timing of intervention is a trial where different anti-arrhythmic drugs were administered, and time to medication administration was a median of 17 minutes after cardiac arrest.[55] Conceivably the time to medication administration may have been too long in to the cardiac arrest to have a meaningful impact. The patients in this trial were also co-enrolled in another trial at the same time, and this may have complicated the processes. Finally, a recent trial of mean arterial blood pressure augmentation yielded neutral results compared to standard of care; however, the intervention was only achieved at approximately 6 hours following ROSC and a median of 2.5 hours following randomization.[56] Implementation of a therapeutic strategy aimed at restoring cerebral oxygen delivery is critically time sensitive and such delay may explain the neutral trial result. Future neuroprotection studies must focus on expeditious implementation of therapeutic interventions following resuscitation. These examples highlight the challenges in research for cardiac arrest and the importance of timely interventions to achieve neuroprotection.

Barriers to translation

The following top 5 barriers to translation were identified and discussed by conference participants during the Neuroprotection Panel (Fig. 2).

1. Patient heterogeneity. Cardiac arrest is the common end to a multitude of highly heterogeneous pathophysiologies and diseases. Patients with cardiac arrest encompass a broad range of underlying causes, comorbidities, and pathophysiology. For example, a prolonged period of hypoventilation leading to hypoxemia and acidosis and then cardiac arrest in a person with opiate intoxication likely has a very different brain injury pattern than a sudden arrhythmia in an otherwise healthy person leading to cardiac arrest. Additionally, the patterns of post-cardiac arrest brain injury vary in the severity of dysfunction in different end-organs, including the brain. Thus, the complexity and variability in patient populations impact the design and generalizability of neuroprotective interventions.

2. Nihilism & lack of knowledge about cardiac arrest. There has been a lot of effort to educate the public about CPR, but there is a broad gap in understanding what happens after a patient has a cardiac arrest and CPR. Low overall survival rates and high rates of neurologic injury are often not discussed and there is a broad lack of patient advocacy supporting this research space. Clinicians also lack experience and expertise in caring for patients with complex post-cardiac arrest physiology and acute disorders of conscious-

WOLF CREEK XVII | Neuroprotection - Top 5 Barriers to Translation

1 Heterogeneity of CA patients: The complexity and variability of patient populations, including different causes of cardiac arrest and comorbidities, impacting the design and generalization of neuroprotective interventions

2 Nihilism & lack of interest/knowledge: There is lack of understanding of the pathophysiology of ischemia-reperfusion injury & lack of knowledge about potential for good outcomes; failure to develop effective therapies has reinforced nihilism

3 Translational pipeline: Insufficient collaboration/methodology/investment in trials, and barriers from large trials needed to prioritize selection of trial agents; use of non-relevant animals; complexity/reproducibility in animal models; biobanking

4 Early and mechanistic biomarkers: Current lack of imaging and non-imaging biomarkers to identify brain injury before and during cardiac arrest management and post-resuscitative care and evaluate mechanisms

5 Neuroprognostication and neuro-triage: When and how to do it so we target interventions to those likely to benefit but don't also inappropriately limit interventions?

Fig. 2 – Neuroprotection: Top 5 barriers to translation as ranked by attendees at Wolf Creek XVII, June 15–17, 2023, Ann Arbor, MI, USA.

ness. The confounding effects of early organ dysfunction and medications on the neurologic exam and biomarkers are often under-appreciated, as is the potential for delayed awakening. Failure of the scientific community to develop effective therapies has reinforced nihilism.

3. Challenges with the translational pipeline: Limitations in pre-clinical, translational, and clinical research thwart efforts to develop new therapies. There is insufficient investment in high-risk and highly innovative research in cardiac arrest. Challenges with poor infrastructure support lead to insufficient collaboration, lack of investments, and insufficient pre-clinical and clinical methodologies. In-person discussion focused on the challenges of funding infrastructure and clinical trial design. Upstream barriers to translation in clinical research for PCABI include the current designs of clinical trials for neuroprotective therapies. Current trial designs include an emphasis on evaluating singular treatment effects across a large population of patients. Critical assumptions are made upon uniform pathophysiologic mechanisms in the study population or equal balancing of these factors in the study groups. Instead, alternate goals of evaluating the efficacy of individual treatment effects could be prioritized. Further, given the various pathophysiologic mechanisms attributed to PCABI, it is unlikely a single intervention will exert a modifiable effect to significantly alter the disease trajectory. Combined or bundled intervention approaches are likely needed. To study such interactions, factorial designs of adaptive trials may be necessary to enhance translation of pre-clinical findings.

From a pre-clinical research standpoint, animal models have been extensively used to study the pathophysiology of PCABI and evaluate the efficacy of promising therapeutics.[57] Although invaluable for controlling experimental conditions, animal models of PCABI have limitations that limit the direct translation of findings to humans.[58–60] First, the typical timeline of animal model experimental studies focuses on hyper-acute phases of PCABI such as the intra-arrest period and immediate post-ROSC phase, i.e. from a few hours up to a few days. It is known that additive injury can continue to occur in PCABI beyond the immediate resuscitative phase and during the hours and days following cardiac arrest. Due to logistical and sometimes ethical constraints in maintaining animal model viability over days, this period of PCABI pathophysiology is not as well described as the immediate phases involving the cardiac arrest and immediate resuscitation. Second, fundamental differences exist in the cellular structure and function of glial cells and the innate immune system

in rodents versus humans.[58] Such fundamental differences likely preclude both the possibility of reproducing in the animal the same brain injury observed in humans and the direct extrapolation of pre-clinical experimental findings to clinical trials. Intermediary translational studies in humans are likely a necessary step to confirm the presence and modifiability of the desired pathophysiologic mechanism attributed to PCABI.

In addition to the above examples, current pathways to develop clinical therapies are long, expensive, highly regulated, and limit the ability to test multiple interventions in a given trial. Critical gaps are outlined further below, but identifying optimal dose, timing and duration of interventions are pervasive limitations that cannot be solved until we concomitantly improve understanding of pathophysiology and mechanisms and develop mechanistic biomarkers. Additionally, systems of care are not currently optimized for improving clinical trial outcomes in cardiac arrest. Opportunities abound to improve pre-hospital and in-hospital resources and teams, meaningfully deploy resources across a health system, and standardize these resources across clinical trial sites.

4. Absence of mechanistic biomarkers: While achieving benefit in patient-centered outcomes is the ultimate goal in cardiac arrest studies, the development of biomarkers that can be obtained early in the post-arrest course, that correlate with underlying physiologic pathways and injury mechanisms is of critical importance to progress research. The development of biomarkers that reflect underlying mechanisms of injury will also help evaluate the efficacy of interventions in the pre-clinical stages. Concomitantly, the establishment of a high-quality biobank is the key to better understanding the pathophysiology of PCABI and identifying potential therapeutic targets. Without the mechanistic biomarkers, we don't know if a therapeutic target is active in any given patient and we can't determine if the therapy as delivered modified the targeted mechanism.

5. Inaccurate Neuro-Triage and Neuroprognostication: The lack of early, acute markers of brain injury severity is considered a significant barrier to further neuroprotection research. Injury patterns and severities vary across patients, and a one-size-fits-all approach to neuroprotection research fails to address this broad range. The efficacy of any intervention would be difficult to measure among a group with great heterogeneity. For example, most patients with mild neurologic injury gain functional recovery irrespective of intervention. Likewise, it would be difficult to alter the outcomes of patients with severe brain injury, especially primary ischemic brain injury, with

any intervention. Therefore, the neuro-triage to find the right patients with "moderate" and modifiable brain injury is the key to translational research. However, methods to quantify and measure the degree of injury early, especially during potential early therapeutic windows, are limited, and this is where the development of biomarkers is critically needed. In addition, neuroprognostication, as it is more commonly thought of as identifying patients likely to have poor outcomes, is flawed and previous studies have a high risk of bias, leading to additional challenges not just quantifying injury but predicting long-term outcomes accurately enough to mitigate inappropriate WLST.

Research priorities

The following top 5 research priorities were identified and discussed by conference participants during the Neuroprotection Panel (Fig. 3).

1. Translational research and trial optimization: Changes to pre-clinical and clinical trial design and methods are needed. An ideal state may include improved pre-clinical models and smaller clinical studies in which interventions can be rapidly tested and discarded or progressed to larger studies. Promising results must necessarily be validated across laboratories and sites, and clinical trial infrastructure that facilitates rapid enrollment of adequate populations is needed. Additionally, post-randomization interventions that are outside of the clinical trial are difficult to measure and likely interact with clinical trajectories, leading to imbalances in care and WLST. Since cardiac arrest patients are not as approachable as other steady or chronic diseases both quantitatively and time-wise for interventional studies, emerging trial designs may have potential roles. An adaptive platform trial is an example, in which the key features of the trial design are modified during the trial in response to accumulating information to maximize statistical efficiency or achieve better outcomes for trial participants.[61] With the power to encompass multiple interventions and primary outcomes in one trial, adaptive trial designs and platform trial infrastructure may contribute to the seamless translation of novel therapies and the shortening of the study period.

2. Addressing patient heterogeneity and individualized interventions: As outlined above, interventions must be tailored to the individual patient's pattern and degree of injury and delivered at the appropriate time post-CA. Characterizing patient heterogeneity would lead to the identification of patients who benefit from therapy and potentially monitor response to therapy, enabling individualized optimization of dose and duration. It could also identify patients for whom a specific therapy will not provide benefit.
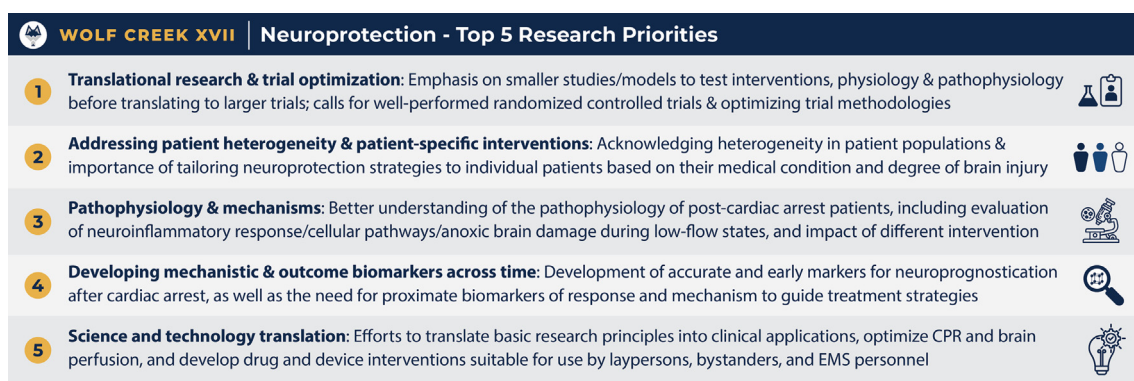
3. Improving understanding of pathophysiology and mechanisms: The group clearly articulated the ongoing importance of supporting mechanistic basic science research to improve understanding of the pathophysiology of PCABI. As mentioned above, accounting for differences in cardiac arrest physiology and patient co-morbidities will be important improvements over existing animal models.

4. Developing mechanistic and outcome biomarkers across post-CA time course: Given the importance of this area as outlined above, this was felt to be an important research priority, with the success of future work predicated on achieving this mission. As discussed in the knowledge gaps section above, the field lacks the understanding of the natural course of PCABI because of the early WLST after perceived poor neurological outcomes. Identifying mechanistic markers and their change over time will shape a better understanding of how to intervene as well as the potential time window to intervene. Mechanistic biomarkers will identify patients likely to benefit (and not benefit) from a therapy, allow monitoring of the response to therapy, and optimize individualized dose and duration. This capability has a critical impact on both clinical trials and translation to patient care.

5. Improving implementation of science and technology: Implementation science is the study of methods to promote integration of evidence-based practices and interventions into routine health care and public health settings.[62] The field studies methods to translate scientific and technological discoveries to ensure delivery to patients and medical professionals and to improve public health. Given the potential impact of neuroprotective methods on patient outcomes, ensuring successful deployment of future discoveries is critical and is also crucial to mitigate healthcare inequities. Opportunities to improve dissemination and uptake of existing science abound, and the successful deployment of future beneficial interventions is critical to success.

Conclusions

This manuscript provides an overview of the Neuroprotection expert panel session during the 2023 Wolf Creek XVII Conference, including the top 5 knowledge gaps, barriers to translation and research priorities identified by conference participants. Neuroprotection after cardiac arrest is often considered a part of the post-arrest care bundle, however, it starts during cardiac arrest with optimizing resuscitation maneuvers, CPR quality, and minimizing time to achieve ROSC,

WOLF CREEK XVII | Neuroprotection - Top 5 Research Priorities

1 Translational research & trial optimization: Emphasis on smaller studies/models to test interventions, physiology & pathophysiology before translating to larger trials; calls for well-performed randomized controlled trials & optimizing trial methodologies

2 Addressing patient heterogeneity & patient-specific interventions: Acknowledging heterogeneity in patient populations & importance of tailoring neuroprotection strategies to individual patients based on their medical condition and degree of brain injury

3 Pathophysiology & mechanisms: Better understanding of the pathophysiology of post-cardiac arrest patients, including evaluation of neuroinflammatory response/cellular pathways/anoxic brain damage during low-flow states, and impact of different intervention

4 Developing mechanistic & outcome biomarkers across time: Development of accurate and early markers for neuroprognostication after cardiac arrest, as well as the need for proximate biomarkers of response and mechanism to guide treatment strategies

5 Science and technology translation: Efforts to translate basic research principles into clinical applications, optimize CPR and brain perfusion, and develop drug and device interventions suitable for use by laypersons, bystanders, and EMS personnel

Fig. 3 – Neuroprotection: Top 5 research priorities as ranked by attendees at Wolf Creek XVII, June 15–17, 2023, Ann Arbor, MI, USA.

and it continues through post-arrest care and in to long-term recovery. Improving the understanding of the pathophysiology, mechanisms, and natural history of PCABI, identifying relevant characteristics of patient heterogeneity, developing real-time physiological monitoring devices, and identifying mechanistic biomarkers will improve research and shape the optimal timing and duration of interventions. These will also yield ways to improve neuro-triage and neuroprognostication, contributing to avoiding premature and inappropriate WLST. This will ultimately lead to tailored precision medicine approaches for neuroprotection after cardiac arrest. Despite success in numerous preclinical studies, no pharmacologic neuroprotective therapy has translated to clinical practice. Nevertheless, the field of cardiac arrest science has never been more exciting. The implementation of new science and technologies and the collaboration of all personnel involved in the field of cardiac arrest will collectively propel the field forward to achieve the goal of improved outcomes after cardiac arrest.

CRediT authorship contribution statement

Karen G. Hirsch: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Tomoyoshi Tamura:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation. **Giuseppe Ristagno:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Mypinder S. Sekhon:** Writing – review & editing, Writing – original draft, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100556.

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