*REVIEW ARTICLE*

Journal of Pre-Clinical and Clinical Research 2022, Vol 16, No 2, 45-53
www.jpccr.eu

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# Cardiac Arrest – An interdisciplinary scoping review of preclinical literature from 2020

**Travis W Murphy[1,A-F], Charles W Hwang[2,B-F], Scott A Cohen[2,A-F], Sarah Gul[3,A-E], Francis Han[4,B-D], Torben K Becker[2,A-F]**

[1] *Cardiothoracic Critical Care, Miami Transplant Institute, University of Miami, USA*
[2] *Department of Emergency Medicine, University of Florida, Gainesville, FL, USA*
[3] *Department of Surgery, Yale University, New Haven, CT, USA*
[4] *Lake Erie College of Osteopathic Medicine, Bradenton, FL, USA*
*A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article*

Travis W Murphy, Charles W Hwang, Scott A Cohen, Sarah Gul, Francis Han, Torben K Becker. Cardiac Arrest: An Interdisciplinary Scoping Review of Preclinical Literature from 2020. J Pre-Clin Clin Res. 2022; 16(2): 45–53. doi: 10.26444/jpccr/150030

## Abstract

**Introduction and Objective.** The Interdisciplinary Cardiac Arrest Research Review (ICARE) group was formed in 2018 to conduct an annual search of peer-reviewed literature relevant to cardiac arrest. Now in its third year, the goals of the review are to illustrate best practices in research and help reduce compartmentalization of knowledge by disseminating relevant advances in the interdisciplinary world of cardiac arrest research. This iteration focuses on pharmacology and basic and translational science contributions.

**Review methods.** A search was conducted of PubMed using keywords related to cardiac arrest. Titles and abstracts were screened for relevance with a focus on basic science and pharmacology. Screened manuscripts underwent standardized scoring of methodological quality and impact on the respective fields by reviewer teams lead by a subject matter expert editor. Articles scoring higher than 99 percentiles by category were selected for full critique. Systematic differences between editors' and reviewers' scores were assessed using Wilcoxon signed-rank test.

**Brief description of the state of knowledge.** The top scoring studies centered around attempts at improving neurologic outcome through improved blood flow and reduction of metabolic demand in order to reduce the impact of hypoxia during resuscitation on the brain.

**Summary.** The sheer number of articles screened is a testament to the need for an accessible source highlighting high-quality and important research. Several high-quality systematic reviews and original research studies have provided a physiologic basis for the treatment of cardiac arrest, and make the case for focused progression of several pharmacologic treatments to larger animal and human trials.

## Key words

epidemiology, emergency medical services, cardiopulmonary resuscitation, heart arrest, out-of-hospital cardiac arrest, sudden cardiac death

## INTRODUCTION AND OBJECTIVE

Recent estimates of the global burden of out-of-hospital cardiac arrest report an annual incidence of 14–147 per 100,000 persons with considerable variability across global regions and age groups [1]. Ongoing improvements in coordinated data collection and novel approaches to care for these patients are continually being presented from social, clinical and pharmacologic perspectives to reduce the significant morbidity and mortality of cardiac arrest. Given the broad scope of cardiac arrest research across multiple disciplines, the Interdisciplinary Cardiac Arrest Research Review (ICARE) Group was created in 2018. This review, now in its third iteration, systematically gathers and summarizes articles in multiple disciplines with relevance or value to the realm of cardiac arrest research in keeping with the PRISMA-ScR guidelines. As a scoping review rather than a systematic review focused on a specific research question, this review is intended to serve as an annual update on high-quality cardiac arrest research. The review reports on the findings related to translational and pre-clinical cardiac arrest research. The intent of the ICARE review is to be a resource both for clinicians and academic researchers by referencing the most important developments from the previous year.

Address for correspondence: Torben K Becker, Department of Emergency Medicine, University of Florida, Gainesville, FL, USA
E-mail: t.becker@ufl.edu

Received: 27.03.2022; accepted:13.05.2022; first published: 06.06.2022

## REVIEW METHODS

The methods for the 2020 ICARE edition are adopted from the Global Emergency Medicine Literature Review group's methodology, as detailed in the procedure manual (Supplement 1) and are consistent with PRISMA-ScR guidelines and the previously published 2019 review [2, 3]. Additional manual screening to prevent inadvertent omissions was also performed. The 2020 ICARE working group is comprised of 67 members, including 54 reviewers, 9 editors, and 4 editorial board members. All editors have previously published cardiac arrest research. The working group consists of physicians, scientists, medical and graduate students from multiple disciplines and educational backgrounds relevant to the field of cardiac arrest. All working group members are unpaid and selected through an application process prior to

literature search. As a scoping review, it was registered on OSFHome as protocol osf.io/4gzbw.

**Literature search.** Publications pertaining to cardiac arrest were searched on PubMed in 2 phases: the first included publications between January and August 2020 and was conducted in October 2020, and the second included publications between September and December 2020 and was conducted in January 2021. To filter by article publication dates, both literature searches were performed using the '[PDAT]' PubMed/MEDLINE field description tag. Therefore, articles with either an 'Electronic Date of Publication' and/or 'Print Date of Publication' in 2020 were included. Inclusion and exclusion criteria were consistent with previous ICARE reviews [2, 4]. Only articles that were available in English were included. Publications that were commentaries, editorials, case reports, study design protocols, data releases, and letters to the editor were excluded. The full PubMed/MEDLINE search query is presented in Supplement 2. We continued to use the refined search string that more precisely identified articles for inclusion for the 2019 edition [2].

**Article screening.** The titles and abstracts of articles identified were screened by the technical and section editors independently based on detailed inclusion and exclusion criteria (Supplement 1). The Kappa Statistic for agreement on article inclusion at this stage was calculated to determine consistency in the screening process. Full texts of selected articles for scoring were classified as either Original Research or Review, according to the study design. The articles were classified into 8 thematic categories. Basic science and pharmacology studies were the focus of this review. The categories of Epidemiology & Public Health, Prehospital Resuscitation, Technology & Care Processes, In-Hospital Resuscitation & Post-Arrest Care Processes, Prognostication & Outcomes, Pediatrics, Interdisciplinary Guidelines & Reviews and COVID-19 are addressed in a parallel manuscript relating to clinical research.

**Article scoring.** Using a predefined scale according to the study type – original research or review – each article was scored independently by reviewers and scores verified by each section editor. Scoring scales for original research and review articles are presented in Tables 1 and 2. In addition to the reviewers' score, each article's 'Impact' and 'Importance' was graded independently by the section editor. Total scores ranged between 0–22 points and calculated using the reviewer 'Clarity' and 'Design' scores and the section editor 'Importance' and 'Impact' scores. To ensure scoring reliability among the working group, random articles were selected and the reviewer and editor scores of each were compared. Systematic differences between editor and reviewer scores for each of these articles were assessed using Wilcoxon signed-rank test.

**Formal article review.** Articles scoring in the 99$^{th}$ percentile by type were evaluated for formal review. To reduce the likelihood of imperfect, but high-impact articles unintentionally being excluded from formal summarization,

**Table 1. S**coring of original research (OR) articles

| Quality Measure | Question | | Points |
|---|---|---|---|
| Design | | | 1 *-or-* |
| A | *Select One* | Descriptive studies (including case studies and case series, natural observation studies and descriptive surveys) | |
| | | Correlation studies (case control studies, prospective observational studies, retrospective studies) | 2 *-or-* |
| | | Non-randomized or non-blinded experimental studies | 3 *-or-* |
| | | Randomized, blinded experimental studies | 4 |
| B | Study design is appropriate to answer the authors' hypothesis. | | 1 |
| C | Correct statistical tests are used to analyze the data. | | 1 |
| D | Results are presented accurately and without bias. | | 1 |
| E | Limitations are *clearly* described, and conclusions supported by data. | | 1 |
| Design Total | | | 8 / Out of max score 8 |
| Ethics | | | 2 |
| A | The study was approved by an institutional review board (IRB)/institutional animal use and care committee, ethics committee, community group, as required by local laws. | | |
| B | Informed consent obtained or consent waived by the IRB (*give point if not applicable, e.g., animal study*). | | 1 |
| C | The authors declare their conflicts of interest or declare that none exist. | | 1 |
| Ethics Total | | | 4 / Out of a max of 4 |
| Importance | | | 2 |
| A | The study results are not specific to one certain patient population, but broadly generalizable to a variety of settings. | | |
| B | The topic being studied is an important one, in that it advances the field of cardiac arrest research or care. | | 2 |
| C | The study is clearly relevant to the realm of cardiac arrest research or care. | | 1 |
| Importance Total | | | 5 / Out of a max of 5 |
| Impact | | | 2 |
| A | The findings or recommendations of this study may feasibly be implemented by practitioners* of cardiac arrest care. | | |
| B | Practitioners* would likely change their practice if they were aware of this study. | | 2 |
| C | The authors of this study raise interesting questions that may stimulate further research. | | 1 |
| Impact Total | | | 5 / Out of a max of 5 |
| | *Practitioner: reader practicing in the category of the article (physician, epidemiologist, pharmacist, etc.) | | |

**Table 2.** Scoring of review (RE) articles

| Quality Measure | Question | Points |
|---|---|---|
| Clarity | | 2 |
| A | The review has a clearly stated hypothesis or purpose. | |
| B | The authors provide sufficient background to place the results of the review into context. | 1 |
| C | The review can be understood by someone with general medical or public health training. | 1 |
| D | The authors use clear language and appropriate graphs, tables, and figures throughout the article. | 1 |
| Clarity Total | | 5 / Out of max score 5 |
| Design | | 3 |
| A | This is a formal meta-analysis or a systematic review that only includes studies with a control group. | |
| B | There is a clear, reproducible method for the selection of studies included in this review. | 2 |
| C | Articles for this review were selected by at least 2 authors blinded to each other's selection. | 1 |
| D | The data was aggregated and/or analyzed appropriately. | 1 |
| Design Total | | 7 / Out of max score 7 |
| Importance | | 2 |
| A | The review is not specific to one certain patient population, but is broadly generalizable to a variety of settings. | |
| B | The topic being reviewed is an important one, in that it advances the field of cardiac arrest research or care. | 2 |
| C | This is clearly relevant to the realm of cardiac arrest research or care. | 1 |
| Importance Total | | 5 / Out of max score 5 |
| Impact | | 2 |
| A | The findings or recommendations of this review appear to have applicability towards improving cardiac arrest research or care. | |
| B | Practitioners* would likely change their practice if they were aware of this review. | 2 |
| C | The authors of this review raise interesting questions that may stimulate further research. | 1 |
| Impact Total | | 5 / Out of max score 5 |
| | *Practitioner: reader practicing in the category of the article (physician, epidemiologist, pharmacist etc.) | |

articles that scored one point below the 99$^{th}$ percentile score were discussed in a committee consisting of 3 editors. Reviewers then summarized these articles with attention to the objective, key findings, and strengths/limitations of each study. Section editors then reviewed summaries for content, accuracy, and style according to each category.

## DESCRIPTION OF THE STATE OF KNOWLEDGE

The screening, scoring, and full article review process is presented in Figure 1. A total of 3,594 articles were identified on initial search; of these, 135 were scored after screening for relevance and deduplication. This included 118 original

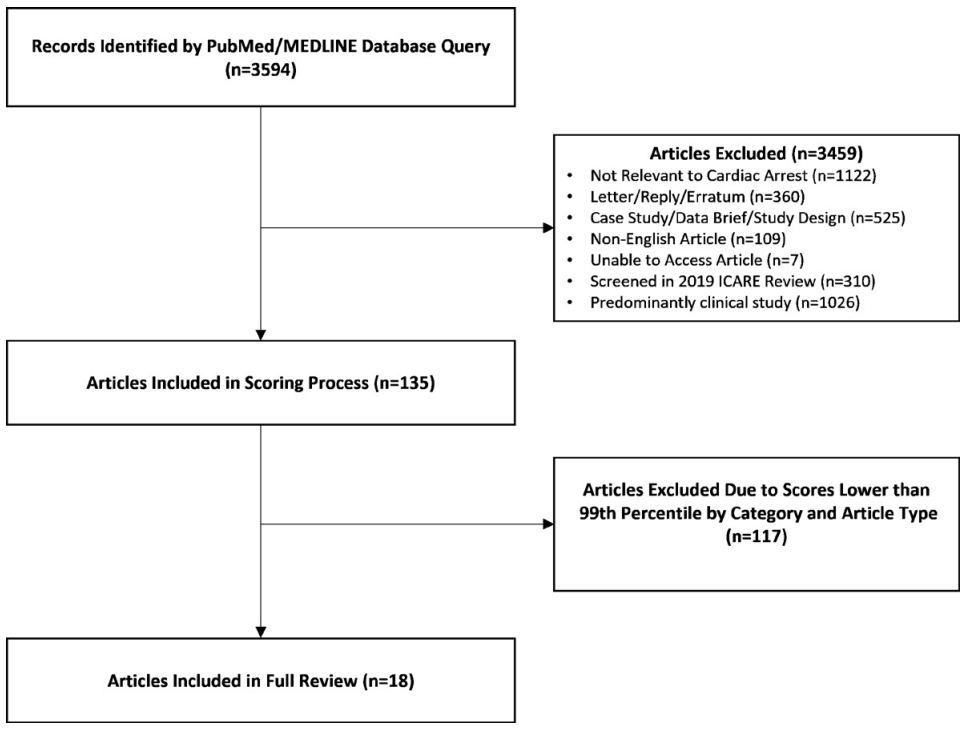


**Figure 1.** Flowchart of screening and scoring processes

**Table 3.** Summary of basic science and pharmacology articles reviewed

| First Author | Title | Journal | Type | Summary |
|---|---|---|---|---|
| Nowadly CD | Zone 3 REBOA does not provide hemodynamic benefits during non-traumatic cardiac arrest | Am J Emerg Med | OR | Use of resuscitative endovascular balloon occlusion of the aorta (REBOA) during CA is a novel approach to restrict cardiac output to the thoracic aortic vasculature, which can improve myocardial and cerebral blood flow. |
| Dogan EM | Resuscitative endovascular balloon occlusion of the aorta in zone 1 versus zone 3 in a porcine model of non-traumatic cardiac arrest and cardiopulmonary resuscitation: a randomized study | Resuscitation | OR | During experimental non-traumatic CA, the systemic blood pressures were higher in REBOA zone 1 compared to zone 3 during CPR, and visceral perfusion from zone 3 occlusion was insignificant long-term. |
| Fumagali F | Ventilation with Argon Improves Survival with Good Neurological Recovery After Prolonged Untreated Cardiac Arrest in Pigs | J Am Heart Assoc | OR | In animal models of CA, ventilation with argon (Ar) has shown replicable neuroprotective and cardioprotective effects |
| Karlis G | Usefulness of F2-isoprostanes in early prognostication after cardiac arrest: a topical review of the literature and meta-analysis of preclinical data | Biomarkers | RE | Plasmal F2-isoprostanes is a prostaglandin-like biomarker of oxidative stress that is formed during ischemia-reperfusion injury (IRI) which correlates to the severity of post-cardiac arrest syndrome (PCAS), and can potentially serve as a novel prognostic tool to predict CA outcome for patients. |
| Duhem H | Improving post-cardiac arrest cerebral perfusion pressure by elevating the head and thorax. | Resuscitation | OR | In critically ill patients, elevation of the head and thorax (EHT) has been found to improve clinical outcomes, with some evidence even suggesting an advantage to EHT during CPR. The optimal head and thorax position after ROSC may increase cerebral perfusion pressure (CerPP) and decrease intracranial pressure (ICP). |
| Olai H | Meta-analysis of targeted temperature management in animal models of cardiac arrest. | Intensive Care Med Exp | RE | TTM has been the standard treatment for OHCA patients with proven benefits on survival and neurological outcome. Numerous durations and depths of therapeutic hypothermia have been shown to be beneficial in animal models of CA and global cerebral ischemia. |
| Zhao H | Amiodarone and/or lidocaine for cardiac arrest: A Bayesian network meta-analysis | Am J Emerg Med | RE | In a meta-analysis of anti-arrythmic drugs utilized during refractory VF or pulseless ventricular tachycardia (pVT), amiodarone use correlated with favourable neurological outcome, while lidocaine use was associated with survival to hospital admission and discharge. |
| Yang M | The Protective Effect of rhBNP on Postresuscitation Myocardial Dysfunction in a Rat Cardiac Arrest Model | Biomed Res Int | OR | In a preclinical CA model, intravenous administration of recombinant human brain natriuretic peptide (rhBNP) provided a cardioprotective effect via TLR4/NF-κB signaling pathway against ischemia/reperfusion injury and improved hemodynamic stability and 24-hr survival rate. |
| Moore JC | Controlled sequential elevation of the head and thorax combined with active compression decompression cardiopulmonary resuscitation and an impedance threshold device improves neurological survival in a porcine model of cardiac arrest | Resuscitation | OR | Combination therapy of controlled sequential elevation (CSE) of head/thorax and active compression-decompression (ACD) CPR with impedance threshold device (ITD) in porcine model of ventricular fibrillation CA demonstrated improved neurological outcomes. |
| Nilsen JH | Study of the effects of 3 h of continuous cardiopulmonary resuscitation at 27 °C on global oxygen transport and organ blood flow | Front Physiol | OR | Continuous cardiopulmonary resuscitation (CPR) at 27 °C showed favorable circulatory effects, as compared to normothermic continuous CPR post cardiac arrest |
| Lind PC | Translation from Animal Studies of Novel Pharmacologic Therapies to Clinical Trials in Cardiac Arrest: A Systemic Review | Resuscitation | RE | A systematic review identifying pre-clinical novel pharmacological therapies and translation of animal studies to clinical trials |
| Piao L | Suppression of Superoxide-Hydrogen Peroxide Production at Site IQ of Mitochondrial Complex I Attenuates Myocardial Stunning and Improves Postcardiac Arrest Outcomes | Crit Care Med | OR | Cardiogenic shock that occurs after CPR often results in mortality. It is proposed to be caused by stunning of myocardial tissue due to an increased generation of mitochondrial free radicals at respiratory complex I, and its severity is dependent on length of no-flow time. This process may be attenuated by a compound known as suppressor of site IQ electron leak (S1QEL) |
| Rysz S | The effect of levosimendan on survival and cardiac performance in an ischemic cardiac arrest model – A blinded randomized placebo-controlled study in swine | Resuscitation | OR | Improved survival and post-ROSC cardiac performance in porcine model of CA following intra- and post-arrest administration of levosimendan versus placebo |
| Shen R | The Effects of Dexmedetomidine Post-Conditioning on Cardiac and Neurological Outcomes After Cardiac Arrest and Resuscitation in Swine | Shock | OR | Dexmedetomidine administration after CA and resuscitation significantly improved cardiac and neurologic outcomes in a swine animal model. |
| Shoaib M | Plasma metabolomics supports the use of long-duration cardiac arrest in rodent model to study human disease by demonstrating similar metabolic alterations | Sci Rep | OR | This article examined the use of rodent models in assessing metabolic injury post-CA by comparing plasma metabolites released in serum by both rats and humans post CA, and demonstrated that rats can function as an acceptable CA research model |
| Jung YH | Effects of Different Doses of Pralidoxime Administered During Cardiopulmonary Resuscitation and the Role of alpha-Adrenergic Receptors in Its Pressor Action | J American Heart Association | OR | A dosage of 40 mg/kg of pralidoxime functioned as a vasopressor, and when administered with epinephrine was beneficial during CPR. This pressor effect was not linked to alpha-adrenoceptors. A higher dose acted as a vasodepressor |
| Yauger YJ | Endotracheal Administered Epinephrine Is Effective in Return of Spontaneous Circulation Within a Pediatric Swine Hypovolemic Cardiac Arrest Model. | Pediatr Emerg Care | OR | Early administration of epinephrine via an established endotracheal tube (ET) is an alternative to intravenous (IV) administration in a pediatric model of hypovolemic CA |
| Zhao Q | Cardiac arrest and resuscitation activates the hypothalamic-pituitary-adrenal axis and results in severe immunosuppression. | J Cereb Blood Flow Metab | OR | Ischemia-reperfusion injury post-CA leads to immune system dysfunction due to activation of the hypothalamic-pituitary-adrenal (HPA) axis by pro-inflammatory cytokines. Therapeutic targeting of this system can resolve immune dysfunction and may improve outcomes. |

research articles and 17 review articles with median score of 18/22 for original research and 16/22 for review articles. Eighteen articles underwent formal critique with summaries available in Supplement 3. Median reviewer scores had good correlation with editor score for both original research articles and review articles. Table 3 summarizes the articles reviewed. The scores for all Original Research and Review articles are presented in Supplements 4 and 5, respectively. No significant differences between editor and reviewer scoring were found among review articles (p=0.697). Among original research articles, section editors scored a median 1 point (IQR: 0–3; p<0.01) less than reviewers. The median and interquartile range of scores by reviewer and editors for each category are presented in Supplement 6.

Preclinical and pharmacologic investigations remained an active area of cardiac arrest research in 2020, with several new insights into the physiologic basis for existing and novel treatments. The following highlights the key findings of the top-scoring articles.

One criticism of animal models in the study of human disease is an inherent difference in anatomy and physiology and, as such, the validity of animal models of human diseases should be taken into consideration when interpreting the findings. A review of mechanical ventilation strategies during chest compressions by Orso et al., which included the results of both clinical and animal models, highlights this discrepancy [5]. Shoaib et al. sought to describe the most appropriate rat model for cardiac arrest by using plasma metabolomics as a marker for severity of metabolic injury. The authors demonstrated that circulating citric acid cycle molecules in rats mirrored circulating levels in humans closely after a 20-minute asphyxia period followed by resuscitation [6]. To model how cardiac arrest affects the hypothalamic-pituitary-adrenal (HPA) axis and leads to immunosuppression, Zhao et al. used a mouse model of cardiac arrest and compared inflammatory cytokines, adrenocorticotropic hormone and leukocyte levels, as well as degrees of intestinal permeability, lung bacterial load and histologic changes to sham mice. The authors used an 8.5 minute cardiac arrest duration and found that cardiac arrest and cardiopulmonary resuscitation (CPR) activated pro-inflammatory cytokines that led to brain inflammation, activation of the HPA axis and elevation of adrenocorticotropic hormone [7]. Secondary analysis using a shorter arrest time treated with either corticosteroids or a glucocorticoid receptor antagonist, found that mice receiving steroids had similar degrees of immune suppression compared to mice undergoing the longer CPR duration, but that mice receiving the glucocorticoid antagonist had fewer effects of immune suppression and improved behavioral test scores [7]. These findings were replicated using an asphyxia model of arrest as well [7]. Overall, these findings suggest that while steroid administration during resuscitation may promote positive outcomes, there may be a mechanism by which ongoing steroid therapy may worsen the inherent immunosuppression seen in cardiac arrest – this provides a physiologic basis for some of the findings suggested in human studies of the effects of steroids in the post-arrest state [8]. In a meta-analysis of targeted temperature management in animal models, Hilmer et al. described the significant heterogeneity in target temperature regimens across studies. The authors also noted that there were differences between the comorbidities of the animals used and the demographics of most human cardiac arrest victims as most subject animals are relatively healthy and have drastically different brain architecture when it comes to rodent models which weakens the translational foundation on which specific treatment regimens for human patients are based [9].

In direct study of the translation of animal studies into human therapies, a sweeping systematic review by Lind et al. identified common themes and gaps in the transition of animal studies into clinical practice. A total of 415 preclinical studies testing 190 different pharmacologic interventions were identified [10]. The authors found that most of these preclinical models did not report neurologic outcomes and noted that only 37% of the studies showed an improvement in survival [10]. Average time of arrest was 8 minutes, suggesting that the studies may not be accurate reflections of human cardiac arrest. An additional analysis of 48 clinical trials showed that 26 of the interventions tested in preclinical trials were tested clinically, with 30 of the trials reporting on neurologic outcomes, but only 13 reporting positive findings [10]. Overall, this study demonstrated the large scale of preclinical and clinical trials for cardiac arrest specifically, and called on researchers to push for an advancement of promising therapies into clinical models and to avoid potentially redundant studies of currently recommended therapies, such as epinephrine and antiarrhythmics [10]. The authors further expressed that that post-arrest therapies such as targeted temperature management that are recommended by guidelines be employed in animal models in an effort to best reflect current clinical practice [10].

A rat model of cardiac arrest explored by Piao et al. presented data that suppressing site IQ electron leak in the mitochondrial complex during CPR led to improved rates of return to spontaneous circulation, reduced levels of reactive oxygen species generation and improved neurologic and myocardial function at 72 hours post-arrest [11]. These findings are compelling in that they provide evidence that attenuation of mitochondrial injury and reactive oxygen species generation during cardiac arrest can lead to meaningful outcomes, and encourages further work on this aspect using larger animal models and mechanistic studies [11]. In another preclinical rat model, recombinant human brain natriuretic peptide (rhBNP) was administered following return of spontaneous circulation (ROSC ) in order to regulate expression of nuclear transcription factor kappa B as a way to attenuate injurious cellular injury pathway [12]. The authors found that animals receiving the rhBNP had improved survival rates at 24 hours post-ROSC, reduced myocardial tissue injury and reduced circulating levels of interleukin 6 and tumor necrosis factor alpha over controls, suggesting a protective effect [12].

Levosimendan was the treatment of interest for a blinded, randomized controlled trial in pigs performed by Rysz et al. After inducing ventricular fibrillation through balloon occlusion of the left anterior descending artery and a 4-minute low-flow time, mechanical CPR was initiated along with a bolus of levosimendan. While an idealized scenario with relatively short ischemia and low-flow times, the rates of ROSC were higher in the treatment arm versus the control arm [13]. Overall, the pigs in the levosimendan group had lower rates of post-arrest death, but there was no significant difference in myocardial scar size upon evaluation by MRI [13]. Research suggesting a beneficial effect of pralidoxime in cardiac arrest has been proposed previously although an effective dose threshold has not yet been determined

and the mechanism by which it potentiates an increase in blood pressure remains unclear [14]. Jung et al. explored the effects of different doses of pralidoxime on the rates of ROSC and cerebral perfusion pressure in a swine model and found that 40mg/kg provided the most benefit. In order to assess the mechanism by which this effect was mediated, the authors then administered adreno-receptor antagonists with phenoxybenzamine resulting in the most pronounced suppression of the pralidoxime effect – suggesting that while pralidoxime results in increased blood pressure, it is not via alpha-adrenergic receptors [14]. While compelling, more detailed mechanistic studies would be needed to demonstrate the effects of pralidoxime on the vasculature more precisely. To compare the efficacy of epinephrine between differing routes of administration, Yauger et al. used a hypovolemic pediatric swine model to compare intravenous with endotracheal administration of epinephrine. This study found that by using the guideline-recommended doses of epinephrine for each route, endotracheal administration led to more frequent ROSC and in a shorter timeframe [15]. This study provides an endorsement of the endotracheal route of administration but should be interpreted in a clinical context as the pigs studied were intubated before the time of arrest. In a meta-analysis of more traditional pharmacologic interventions, Zhao et al. examined the associations of both lidocaine and amiodarone with survival to hospital admission or discharge and neurologic outcome. The authors found that while lidocaine was associated with increased rates of survival, neurologic outcomes in patients receiving amiodarone were better [16]. While these findings suggest that there may be a benefit of one antiarrhythmic over another, a physiologic basis for the difference in outcomes between the medications was not suggested, and a 2016 trial comparing lidocaine and amiodarone directly showed that outcomes were similar between these medications [17]. In another study evaluating the use of dexmedetomidine, a drug that is already in common clinical practice, Shen et al. examined the effects of dexmedetomidine on outcome post-arrest given its $\alpha_2$-receptor agonist properties. Twenty-eight pigs undergoing an 8-minute cardiac arrest and 5-minute resuscitation, following AHA guidelines, were divided into control, low-dose and high-dose dexmedetomidine groups for post-arrest care [18]. Myocardial function, neurologic deficit score, and serum biomarkers of cardiac and cerebral injury were compared across all groups, with a suggestion of dose-dependent benefit to dexmedetomidine being seen [18]. This study expands on a previous study in rats, and while the lack of histologic evaluation and typical limitations of using otherwise healthy animals to model cardiac arrest may limit the generalizability of these findings, human study may be feasible given the availability of dexmedetomidine as a sedative [18].

Models testing different methods to manipulate the distribution of blood flow were also prevalent among the articles included in this year's edition. Rather than using pharmacologic means to increase cerebral perfusion pressures, 2 studies evaluated the use of resuscitative endovascular balloon occlusion of the aorta (REBOA) as a method for directing blood flow to only the most vital organs [19, 20]. In both of these studies, pigs were induced into cardiac arrest with balloon occlusion in either the zone 1 or zone 3 positions. Both studies concluded that zone 3 occlusion was not associated with a meaningful increase in perfusion to the brain or an associated increase in rate of ROSC [19, 20]. In a direct test of head and thorax elevation during active chest compressions, Moore et al. found that coronary and mean arterial pressures, end-tidal CO2 and rates of ROSC were all more favorable in pigs that underwent controlled sequential elevation following 10 minutes of untreated ventricular fibrillation, compared with those who remained supine throughout the resuscitation. Another study of head and thorax elevation in the immediate post-arrest period suggested similar benefits with decreased intracranial pressure (ICP) and increased cerebral perfusion pressures noted [21]. Taken together, these data provide a mechanistic evaluation of sequential elevation and its effects on post-arrest outcomes, supporting conclusions suggested by clinical trials [21, 22]. As an easily implementable change assuming adequate resuscitation, further investigation of head-up positioning in the peri-arrest period is warranted.

In an expansion of the use of noble gasses in the care of patients following cardiac arrest, Fumagalli et al. used different concentrations of the gas argon and found that pigs resuscitated with argon gas had increased rates of neurologically intact survival in a dose-responsive relationship [23]. Pigs treated with argon gas were also noted to have lower circulating levels of biomarkers for brain injury, and a decreased concentration of neurotoxin kynurenine metabolites in comparison to controls [23]. While this study marks encouraging progress in the use of noble gasses in the resuscitation of cardiac arrest victims, the relatively small sample size of 36 pigs and lack of standard post-arrest therapies being incorporated obscures the extent of clinical impact that can be expected [23, 24].

In a purely physiologic study of organ blood flow during CPR, Nilsen et al. compared cardiac output, mean arterial pressure, global oxygen transport and blood flow to the kidneys, liver, brain, and viscera between pigs at normal body temperature versus those in hypothermic arrest. Blood flow to organs was quantified by the use of radiolabeled microspheres injected into the left ventricle and detected using neutron activation [25]. Pigs at normothermia received 45 minutes of continuous CPR, whereas the hypothermic pigs received continuous CPR for 3 hours [25]. The authors found unaltered blood flow in the hypothermic pigs until the one-hour mark whereas organ blood flow decreased with a corresponding increase in serum lactate in normothermic pigs after 15 minutes [25]. Organ blood flow to the brain, heart and intestines did not decrease until the 3 hour mark in hypothermic pigs [25].

Animal models have suggested the utility of F2-isoprostane levels as a predictor of outcomes after previous cardiac arrest, and a review by Karlis et al. sought to quantify the utility of this biomarker for clinical use. Upon pooling data from 13 preclinical studies and one clinical study involving cardioplegia during cardiac surgery, the authors noted that this biomarker rose as early as 5 minutes and persisted for a number of hours before plateauing, suggesting that it may be helpful in quantifying the degree of ischemia reperfusion injury [26].

**Limitations.** The 2020 Interdisciplinary Cardiac Arrest Research Review is not without limitation, including a significant heterogeneity in the nature of the studies included, and a lack of association with neurologic outcome after the 72-hour mark recommended in current guidelines [4, 26–29]. Further research dedicated to the association of given levels

with degrees of injury and recovery after cardiac arrest in a clinical context will be needed to determine the prognostic significance of these laboratory values.

Additionally, the conclusions presented are descriptive of the current evidence for various preclinical topics in cardiac arrest research, but are insufficient to be considered comprehensive. The aim of this literature review was to highlight advances in the field of cardiac arrest medicine on an annual basis. An intrinsic shortcoming of this approach is that it does not provide such an exhaustive context such as historical comparison seen in a systematic review. To address this concern, we provide article summaries and commentaries for additional context in Supplement 3. Secondly, while the methodology used to screen, score, and select articles is designed to capture the most relevant research, it is possible that other high-quality publications may have been inadvertently omitted. Lastly, to remain objective in this literature search, this review did not include letters to the editor, commentaries, and other editorials which could provide additional context when interpreting the impact of larger or more controversial studies.

## SUMMARY

In its third year, the Interdisciplinary Cardiac Arrest Research Review scored more than a 1,000 articles related to cardiac arrest, and after a rigorous scoring process, fully summarized 18 articles in the category of Basic Science and Pharmacology. Manuscripts with a clinical focus were addressed in a parallel manuscript from the same ICARE group. While COVID-19 featured heavily in the scientific literature throughout 2020, high-quality preclinical research relating to both COVID-19 and cardiac arrest specifically has yet to be published. The top scoring studies centered around attempts at improving neurologic outcome through improved blood flow and reduction of metabolic demand in order to reduce the impact of hypoxia during resuscitation on the brain. The total number of articles relevant to cardiac arrest continues to demonstrate the need for an accessible guide that summarizes findings of quality research articles to serve as a reference for clinicians and scientists. ICARE's goal is to further the development of the field of cardiac arrest medicine by highlighting the most methodologically sound and practice-changing articles on an annual basis.

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## Appendix

Appendix A: Interdisciplinary Cardiac Arrest Research Review (ICARE) 2020 Managing Editors, Editors, and Reviewers:

| Name | Degrees | Role | Category | Affiliation 1 | Affiliation 2 |
|---|---|---|---|---|---|
| Torben K. Becker | MD, PhD, RDMS | Editor-in-Chief | Executive Committee | University of Florida, College of Medicine, Department of Emergency Medicine | |
| Travis W. Murphy | MD | Managing Editor | Executive Committee | Cardiothoracic Critical Care, Miami Transplant Institute, University of Miami | |
| Charles W. Hwang | MD | Editor | In-Hospital Resuscitation & Post-Arrest Care Processes | University of Florida, College of Medicine, Department of Emergency Medicine | |
| Sarah Gul | MD | Editor | Basic Science & Pharmacology | Yale University, Yale School of Medicine, Department of Surgery | |
| Scott Cohen | BS | Technical Editor | Executive Committee, Technical Committee | University of Florida, College of Medicine, Department of Emergency Medicine | |
| Francis Han | BS | Assistant Technical Editor | Technical Committee | Lake Erie College of Osteopathic Medicine, Bradenton, FL | |
| Morgan W. Carson-Marino | MS | Reviewer | Basic Science & Pharmacology | University of Florida, College of Pharmacy | University of Florida, College of Medicine, Department of Physiology and Functional Genomics, Department of Anesthesiology, Center for Translational Research in Neurodegenerative Disease (CTRND) |
| Colton B Amaral | BS | Reviewer | Basic Science & Pharmacology | University of Central Florida, College of Medicine | |
| Megan Rivera | MD | Reviewer | Basic Science & Pharmacology | University of Florida, College of Medicine, Department of Emergency Medicine | |
| Bethany Kavalakatt | BS | Reviewer | Basic Science & Pharmacology | Lake Erie College of Osteopathic Medicine, Bradenton, FL | |
| Saketh Narahari | BS | Reviewer | Basic Science & Pharmacology | Lake Erie College of Osteopathic Medicine, Bradenton, FL | |
| Stefan Anthony | BA | Reviewer | Basic Science & Pharmacology | Lake Erie College of Osteopathic Medicine, Bradenton, FL | |

On behalf of the Interdisciplinary Cardiac Arrest Research Review ICARE Group