Available online at www.sciencedirect.com

Resuscitation Plus

journal homepage: www.elsevier.com/locate/resuscitation-plus

Review

Animal research in cardiac arrest

Lars W. Andersen[a,b,c,d], *Lauge Vammen*[a], *Asger Granfeldt*[a,b,*]

Abstract

The purpose of this narrative review is to provide an overview of lessons learned from experimental cardiac arrest studies, limitations, translation to clinical studies, ethical considerations and future directions.

Cardiac arrest animal studies have provided valuable insights into the pathophysiology of cardiac arrest, the effects of various interventions, and the development of resuscitation techniques. However, there are limitations to animal models that should be considered when interpreting results. Systematic reviews have demonstrated that animal models rarely reflect the clinical condition seen in humans, nor the complex treatment that occurs during and after a cardiac arrest. Furthermore, animal models of cardiac arrest are at a significant risk of bias due to fundamental issues in performing and/or reporting critical methodological aspects. Conducting clinical trials targeting the management of rare cardiac arrest causes like e.g. hyperkalemia and pulmonary embolism is challenging due to the scarcity of eligible patients. For these research questions, animal models might provide the highest level of evidence and can potentially guide clinical practice.

To continuously push cardiac arrest science forward, animal studies must be conducted and reported rigorously, designed to avoid bias and answer specific research questions. To ensure the continued relevance and generation of valuable new insights from animal studies, new approaches and techniques may be needed, including animal register studies, systematic reviews and multilaboratory trials.

Keywords: Animals, Cardiac arrest, Cardiopulmonary resuscitation, Preclinical, Experimental

Introduction

Experimental animal research has played a significant role in almost every medical breakthrough in the last 100 years, including within cardiac arrest research. Interestingly, early cardiac arrest studies were performed on humans volunteers due to a lack of regulations with regards to the protection of human subjects in research. This included the concept of mouth-to-mouth ventilation being tested on sedated and paralyzed human volunteers.[1] The importance of animal studies increased with the development of research ethics for humans in the 1970s, making experimental animal research an essential aspect for improving outcomes for cardiac arrest patients. Experimental animal research allows the researcher to address a variety of scientific questions from studies on physiology to the discovery of new therapeutic approaches, not possible in humans. However, the majority of results obtained in preclinical models cannot be reproduced or translated to humans, which has put animal research in a bad light and made some people refute any value to animal research.[2,3] This narrative review will provide an overview of lessons learned from experimental cardiac arrest studies, limitations, translation to clinical studies, ethical considerations and future directions.

What have we learned from cardiac arrest animal studies

Cardiac arrest animal studies have provided valuable insights into the pathophysiology of cardiac arrest, the effects of various interventions, and the development of resuscitation techniques. Refuting the value of animal research would have deprived modern cardiopulmonary resuscitation (CPR) of some of the most important interventions. The two most important cardiac arrest interventions, chest compressions and defibrillation, were developed and tested in animals.[4,5] Animal studies have also provided valuable insight into the potential beneficial and harmful effects of ventilation during CPR.[6,7] Furthermore, animal studies have been valuable in the development of mechanical chest compressions devices, which have subsequently been tested in clinical trials.[8–11]

Similar, the use of adrenaline during cardiac arrest is based on numerous animal studies testing different aspect of adrenaline administration during CPR.[12,13] The concept of post-resuscitation disease, later named the post-cardiac arrest syndrome, is based on findings from animal studies.[14,15] Animal studies have discovered important aspects such as delayed neuronal death, selective neural

* Corresponding author at: Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Denmark.
E-mail address: granfeldt@clin.au.dk (A. Granfeldt).

https://doi.org/10.1016/j.resplu.2023.100511

death, myocardial stunning and pathophysiological mechanisms that later has been targeted in clinical trials. Animal studies have also been crucial in advancing our understanding of pediatric resuscitation, a population where large, randomized trials are difficult to perform. Due to lack of clinical data, pediatric guidelines repeatedly cite animal studies to inform clinical practice.[16] Furthermore, the concept of a hemodynamic-directed approach to pediatric CPR was developed and tested in the animal laboratory and later tested in clinical studies.[17–19] These examples illustrate the importance of experimental cardiac arrest research. The interventions mentioned above, except for adrenaline, are all techniques and physiological approaches, illustrating a challenge with translation of novel pharmacological interventions to clinical use.[20]

Challenges with animal studies

While animal studies play an important role in resuscitation research, translation of findings from animal studies to humans can be challenging. Conceptually, the lack of translation might be explained by one or more of three factors: 1) An inherent physiological difference between animals and humans that makes translation difficult irrespective of other factors,[21,22] 2) a discrepancy between the clinical condition in humans and the current animal models, or 3) problems with the validity of animal studies due to methodological shortcomings. While the last two are potentially modifiable, the first is not. Since the first factor is not specific to cardiac arrest, it will not be discussed further here. The other two will be discussed in more detail below.

Do animal models reflect clinical reality?

Patients with cardiac arrest are heterogenous, with underlying comorbidity, multiple different cardiac arrest etiologies, and varying degrees of disease severity in the post-cardiac arrest phase ranging from stable and awake patients to comatose patients with multiorgan failure. This heterogeneity not only poses a challenge for clinical trials in humans, it also makes animal studies, aiming to reflect the clinical condition of cardiac arrest in humans, difficult.

In a review article from 2017, the authors examined all cardiac arrest animal studies published between 2011 and 2016.[23] The authors identified 490 studies published in 154 different journals. Contrary to humans with cardiac arrest, which often have significant comorbidity,[24] animals included in the studies were almost always (97%) healthy prior to the cardiac arrest.[23] Cardiac arrest was induced by electric pacing in approximately half of the studies, while 25% used asphyxia. Only 2% of the studies induced cardiac arrest with a myocardial infarction, one of the most common causes of cardiac arrest in humans.[25,26] In half of the studies, the animals were defibrillated although a shockable rhythm is only present in approximately 20% of human cardiac arrests.[24] Very few studies included post-cardiac arrest care (e.g., targeted temperature management, use of vasopressor) and many studies only included a short observation period (median of 24 hours). Taken together, the review found that the included animal models rarely reflected the clinical condition seen in humans, nor the complex treatment that occurs during and after cardiac arrest.

While it is impossible that animal models should fully reflect the human condition, as this would make experiments almost impossible to conduct, it is likely that more realistic animal models would allow for better translation of findings to the clinical setting. The complexity of the animal model should reflect the research question. If the primary interest is in pathophysiological mechanisms, it might be desirable to have a simpler model with less heterogeneity. However, if the interest is in the effect of certain interventions on clinical outcomes (e.g., return of spontaneous circulation, survival, neurological outcomes) prior to translation to human trials, a more complex model better reflecting the human condition might be preferable. Inevitably, more complex models will result in increased heterogeneity and therefore likely a need for animal studies with larger sample sizes.

Are animal studies biased?

Clinical trials in humans are often conducted according to a registered and approved detailed protocol with a focus on optimizing internal validity. Unfortunately, the standards for the conduct and reporting of animal studies have not been as high.

In a follow-up to the previous mentioned review, the authors examined reporting and bias in a random sample of 100 interventional animal studies.[27] The review found that most studies used randomization, but the methodology was unknown or insufficiently reported in approximately two thirds of the studies. Blinding was not reported or performed in approximately half of the studies and two thirds did not have blinding of outcome assessors. 80% of all studies lacked a sample size calculation, while 70% did not have a specified primary outcome. These findings are concerning, and the review concluded "... animal models of cardiac arrest are at a significant risk of bias due to fundamental issues in performing and/or reporting critical methodological aspects such as randomization and blinding."[27] Adequate performance and reporting of randomization and blinding are key elements to avoid bias in animal studies and should be the gold standard.

It is possible that selective outcome reporting and publication might also be a cause of the lack of reproducibility of animal studies. These issues cause an inflation of the Type 1 error rate (i.e., more false positive results). Increased rigor in reporting and preregistration of animal studies might mitigate some of these issues. The ARRIVE guidelines was developed as a tool to ensure transparent reporting af animal studies with sufficient details that allows for a thorough assessment of the methods used (Table 1).[28] The guidelines consist of a checklist to be included with publication and, although endorsed worldwide, adherence to the guidelines has been inconsistently used. Disease specific guidelines can also help bolster and refine the methodology of pre-clinical investigations. Contemporary guidelines for experimental studies have been created for example for sepsis, heart failure and stroke.[29–31] For cardiac arrest the core aspects included in the experimental Utstein guidelines from 1996 are still valid (Table 1). However, the recommendations mostly include intra-arrest resuscitative efforts and many of the recommendations are outdated and imprecise.[32] An update for the experimental reporting and conducing guidelines for cardiac arrest animal studies is warranted.

An additional tool to be utilized to strengthen the methodology of preclinical studies is publication of protocols prior to completing the study (e.g., preclinicaltrials.eu).[33] This can help to increase transparency and reduce reporting bias including bias induced by selective outcome reporting.

Table 1 – Resources for conducting experimental animal research.	
Animal Welfare	Guide for the Care and Use of Laboratory Animals[50] National Centers for the Replacement, Refinement & Reduction of Animals in Research
Reporting & Registration	Animal Research: Reporting of In Vivo Experiments (ARRIVE) Guidelines[23] Utstein-Style Guidelines for Uniform Reporting of Laboratory CPR Research[27] Trial registration: https://www.preclinicaltrials.eu
Review & bias	Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE)[51] SYRCLE's risk of bias tool for animal studies[44]

Key takeaway messages

The type and complexity of the animal model should reflect the research question.

Animal studies should be performed rigorously to avoid bias.

Adherence to the ARRIVE guidelines ensures thorough reporting.

Publication of protocols should be considered to ensure transparent reporting.

Multilaboratory preclinical studies, systematic reviews and animal register studies are methods to ensure the continued relevance of animal studies.

Translation of findings from animal studies

As mentioned, animal models have historically led to great discoveries still in use during and after cardiac arrest. Unfortunately, looking beyond the general improvements in CPR and intensive care, no novel interventions specifically improving outcomes for cardiac arrest victims have been discovered during the last decades. This is despite a large number of clinical trials being conducted.[34] We know from other fields of research that animal experiments potentially can guide decision making whether or not to conduct a clinical trial.[35] This is immensely important as clinical trials in the setting of cardiac arrest are ethically, economically and logistically challenging to perform. A recent systematic review of all cardiac arrest animal studies testing pharmacological intervention within a 20-year period, sought out to investigate whether animal experiments are utilized as a stepping-stone to clinical testing within the field of cardiac arrest and to look for novel promising interventions.[36]

The systematic review revealed 415 cardiac arrest animal studies testing 190 different pharmacological interventions administered after the onset of cardiac arrest. Using the list of interventions tested in animal models, another systematic review was conducted looking at clinical trials testing the identified interventions. This showed that 26 different interventions were tested in 43 different trials. Overall, the review showed that animal studies had a potential for finding novel interventions. Approximately one third of all animal studies in the review reported improvement in clinically relevant outcomes (return of spontaneous circulation and survival). Of most interest was that several interventions, e.g. glibenclamide and nitric oxide showed positive effects on clinically relevant outcomes in more than five different animal investigations, but never have been tested in clinical trials. The systematic review showed examples of several interventions that were tested in clinical trials although showing no positive effect in animal studies. This illustrates the need for the clinical researchers testing novel interventions to be aware of the results from experimental studies and that clinical researchers may prematurely conduct clinical trials without sufficient preclinical data. As an example, a clinical trial was conducted testing the effects of cyclosporine in post-cardiac arrest patients without any cardiac arrest animal studies being published prior to initiation of the trial.[37] Similarly, a recent single experimental study demonstrated protective effects of hypertonic sodium lactate infusion in a pig model of experimental cardiac arrest.[38] Although several important questions remain regarding timing, duration of infusion, dose and whether it is lactate, hypertonic sodium or the combination that is potentially protective, the authors are already proceeding to a phase II clinical trial (NCT05004610). These two examples illustrate that the failures to translate findings from preclinical models may also be caused by premature testing in clinical trials.

Ethical considerations

Experimental animal research should be conducted according to regulations and guidelines and reported according to journal requirements and the ARRIVE guidelines. The 3Rs, replacement, reduction, and refinement, are guiding principles in the field of animal research and experimentation. Replacement emphasizes finding alternatives to the use of animals in research whenever possible. As the ultimate goal is to replace animal experiments with methods that do not involve animals, this may challenge the use of animals in research in the future. Reduction focuses on minimizing the number of animals used in experiments including the use of sample size

calculations. Studies with a limited number of animals can, however, be a waste as they provide no definite answer to the specific research question. As stated above, 80% of all studies lacked a sample size illustrating a need for improvement. Refinement is about improving the welfare and conditions of animals that must be used in research. Setting up strict protocols for the acclimatization and care taking of animals may benefit both the refinement requirement and the strive for clinical relevance.[39] Refinement is especially ethically challenging when conducting survival studies, where the aim often is to reproduce severe neurological function as is seen clinically. The importance of clinical relevance is here balanced against requirements to minimize any pain, distress, or suffering.

The future of animal studies

To ensure the continued relevance and generation of valuable new insights from animal studies, it may be necessary to reconsider the approaches and techniques employed. This could include refinement of experimental procedures to avoid bias, more clinically relevant animal models and experiments, and new approaches such as animal register studies, systematic reviews and multilaboratory trials.

Multilaboratory preclinical studies have been suggested as a method to improve reproducibility, generalizability and issues with small sample sizes.[40,41] In a systematic review from 2023, 16 multicenter animal studies across all research disciplines were identified.[42] Twelve of 16 studies were published in 2015–2020 illustrating an increased focus in the recent years. Interestingly, the review identified that study quality was higher for multilaboratory studies versus single laboratory studies, although none of the identified multilaboratory had low risk of bias. Within the field of cardiac arrest only one multilaboratory study, known by the authors, has been published.[43] The study was a multicenter, double-blinded, placebo-controlled preclinical cardiac arrest trial testing the effect of adrenaline boluses or infusion during CPR. The trial included five different laboratories, with each laboratory including nine pigs. The multilaboratory study demonstrated no effect of adrenaline either as a bolus or infusion on coronary perfusion pressure, however with a markedly different response across the five laboratories. This illustrates the tradeoff between increased external validity at the cost of increased heterogeneity and potentially smaller effect sizes in multilaboratory studies. Although multilaboratory studies seems compelling, one of the major barriers is the establishment of a consistent protocol, with attention to exact experimental details across research labs and subsequent protocol adherence. This will reduce heterogeneity but at the cost of external validity.[42] This is also illustrated in the cardiac arrest multilaboratory study where experimental procedures such as anesthesia and chest compression techniques differed between laboratories. Furthermore, multilaboratory studies are costly and whether they improve identification of treatments that results in successful clinical translation is unknown.

An alternative to interventional multilaboratory studies is animal register studies where already collected data is combined and compared across laboratories. This makes comparison of physiological data and outcomes measures across models possible, which may display variation between laboratories. This process could also be preparatory for multilaboratory studies by identifying important discrepancies between laboratories.

Systematic reviews are a comprehensive and rigorous method to gather, analyze, and synthesize existing research evidence on a specific research question. The number of systematic reviews addressing clinical questions have increased dramatically over time. Within pre-clinical studies initiatives such as The Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Studies (CAMARADES) and Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) has brought attention to preclinical systematic reviews and modified the methodology to experimental animal studies (Table 1).[44] As an example, Olai et al. performed a comprehensive systematic review of targeted temperature management in animal models of cardiac arrest.[45] The review identified that targeted temperature management was superior to control under most experimental conditions, but also that substantial between-study heterogeneity existed and that study quality generally was low to moderate, in accordance with our previous reviews. If a sufficient number of preclinical studies exist within a given topic systematic reviews of preclinical studies prior to clinical trials could provide valuable information.

Although clinical randomized trials provide the highest level of evidence, not all questions can be addressed in clinical trials. For example, specific treatments for rare causes of cardiac arrest (e.g., hyperkalemia, pulmonary embolism, toxicological causes) are difficult to address in clinical trials due to the limited number of patients. For these research questions, animal models might provide the highest level of evidence and can potentially guide clinical practice. As an example, animal models have been developed that mimic different causes of cardiac arrest to address specific research questions for each cause, that cannot be answered in a clinical trial.[46–49]

Conclusion

To continuously push cardiac arrest science forward, animal studies must be conducted and reported rigorously, designed to avoid bias and answer a specific research question. To ensure the continued relevance and generation of valuable new insights from animal studies, new approaches and techniques may be needed, including animal register studies, systematic reviews and multilaboratory trials.

CRediT authorship contribution statement

Lars W. Andersen: Conceptualization, Writing – review & editing. **Lauge Vammen:** Conceptualization, Writing – review & editing. **Asger Granfeldt:** Conceptualization, Writing – review & editing.

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.

Funding

Asger Granfeldt was supported by a grant from the Health Research Foundation of Central Denmark Region.

Author details

[a]Department of Anesthesiology and Intensive Care Medicine, Aarhus University Hospital, Aarhus, Denmark [b]Department of Clinical Medicine, Aarhus University, Denmark [c]Department of Anesthesiology and Intensive Care, Viborg Regional Hospital, Viborg, Denmark [d]Prehospital Emergency Medical Services, Central Region Denmark, Denmark

REFERENCES

1. Safar P. Ventilatory efficacy of mouth-to-mouth artificial respiration: airway obstruction during manual and mouth-to-mouth artificial respiration. J Am Med Assoc 1958;167:335–41.
2. Baker M. 1,500 scientists lift the lid on reproducibility. Nature 2016;533:452–4.
3. McNutt M. Journals unite for reproducibility. Science 2014;346:679.
4. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. JAMA 1960;173:1064–7.
5. Kouwenhoven WB. The development of the defibrillator. Ann Intern Med 1969;71:449–58.
6. Markstaller K, Karmrodt J, Doebrich M, et al. Dynamic computed tomography: a novel technique to study lung aeration and atelectasis formation during experimental CPR. Resuscitation 2002;53:307–13.
7. Idris AH, Becker LB, Fuerst RS, et al. Effect of ventilation on resuscitation in an animal model of cardiac arrest. Circulation 1994;90:3063–9.
8. Steen S, Liao Q, Pierre L, Paskevicius A, Sjoberg T. Evaluation of LUCAS, a new device for automatic mechanical compression and active decompression resuscitation. Resuscitation 2002;55:285–99.
9. Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. JAMA 2014;311:53–61.
10. Wik L, Olsen JA, Persse D, et al. Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial. Resuscitation 2014;85:741–8.
11. Halperin HR, Paradis N, Ornato JP, et al. Cardiopulmonary resuscitation with a novel chest compression device in a porcine model of cardiac arrest: Improved hemodynamics and mechanisms. J Am Coll Cardiol 2004;44:2214–20.
12. Redding JS, Pearson JW. Evaluation of drugs for cardiac resuscitation. Anesthesiology 1963;24:203–7.
13. Berg RA, Otto CW, Kern KB, et al. High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: a prospective, randomized study. Crit Care Med 1994;22:282–90.
14. Negovsky VA. Postresuscitation disease. Crit Care Med 1988;16:942–6.
15. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 2008;118:2452–83.
16. Van de Voorde P, Turner NM, Djakow J, et al. European resuscitation council guidelines 2021: paediatric life support. Resuscitation 2021;161:327–87.
17. Morgan RW, Kilbaugh TJ, Shoap W, et al. A hemodynamic-directed approach to pediatric cardiopulmonary resuscitation (HD-CPR) improves survival. Resuscitation 2017;111:41–7.
18. Lautz AJ, Morgan RW, Karlsson M, et al. Hemodynamic-directed cardiopulmonary resuscitation improves neurologic outcomes and mitochondrial function in the heart and brain. Crit Care Med 2019;47:e241–9.
19. Berg RA, Morgan RW, Reeder RW, et al. Diastolic blood pressure threshold during pediatric cardiopulmonary resuscitation and survival outcomes: a multicenter validation study. Crit Care Med 2023;51:91–102.
20. 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.
21. Shanks N, Greek R, Greek J. Are animal models predictive for humans? Philos Ethics Humanit Med 2009;4:2.
22. Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A 2013;110:3507–12.
23. Vognsen M, Fabian-Jessing BK, Secher N, et al. Contemporary animal models of cardiac arrest: a systematic review. Resuscitation 2017;113:115–23.
24. Hoybye M, Stankovic N, Holmberg M, Christensen HC, Granfeldt A, Andersen LW. In-hospital vs. out-of-hospital cardiac arrest: patient characteristics and survival. Resuscitation 2021;158:157–65.
25. Myat A, Song KJ, Rea T. Out-of-hospital cardiac arrest: current concepts. Lancet (London, England) 2018;391:970–9.
26. Allencherril J, Lee PYK, Khan K, Loya A, Pally A. Etiologies of In-hospital cardiac arrest: a systematic review and meta-analysis. Resuscitation 2022;175:88–95.
27. Fabian-Jessing BK, Vallentin MF, Secher N, et al. Animal models of cardiac arrest: a systematic review of bias and reporting. Resuscitation 2018;125:16–21.
28. Percie du Sert N, Hurst V, Ahluwalia A, et al. The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biol 2020;18:e3000410.
29. Osuchowski MF, Ayala A, Bahrami S, et al. Minimum quality threshold in pre-clinical sepsis studies (MQTiPSS): an international expert consensus initiative for improvement of animal modeling in sepsis. Shock (Augusta, Ga) 2018;50:377–80.
30. Houser SR, Margulies KB, Murphy AM, et al. Animal models of heart failure: a scientific statement from the American Heart Association. Circ Res 2012;111:131–50.
31. Fisher M, Feuerstein G, Howells DW, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke 2009;40:2244–50.
32. Idris AH, Becker LB, Ornato JP, et al. Utstein-style guidelines for uniform reporting of laboratory CPR research. A statement for healthcare professionals from a task force of the American Heart Association, the American College of Emergency Physicians, the American College of Cardiology, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Institute of Critical Care Medicine, the Safar Center for Resuscitation Research, and the Society for Academic Emergency Medicine. Writing Group. Circulation 1996;94:2324–36.
33. Vammen L, Johannsen CM, Baltsen CD, et al. Thiamine for the treatment of cardiac arrest-induced neurological injury: a randomized, blinded, placebo-controlled experimental study. J Am Heart Assoc 2023:e028558.

34. 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.
35. Horn J, de Haan RJ, Vermeulen M, Luiten PG, Limburg M. Nimodipine in animal model experiments of focal cerebral ischemia: a systematic review. Stroke 2001;32:2433–8.
36. 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 2020.
37. Argaud L, Cour M, Dubien PY, et al. Effect of cyclosporine in nonshockable out-of-hospital cardiac arrest: the CYRUS randomized clinical trial. JAMACardiol 2016;1:557–65.
38. Annoni F, Su F, Peluso L, et al. Hypertonic sodium lactate infusion reduces vasopressor requirements and biomarkers of brain and cardiac injury after experimental cardiac arrest. Crit Care 2023;27:161.
39. Thomsen AF, Kousholt BS. Transition of farm pigs to research pigs using a designated checklist followed by initiation of clicker training – a refinement initiative. J Vis Exp 2021.
40. Jones SP, Tang X-L, Guo Y, et al. The NHLBI-Sponsored Consortium for preclinicAl assESsment of cARdioprotective Therapies (CAESAR). Circ Res 2015;116:572–86.
41. Llovera G, Hofmann K, Roth S, et al. Results of a preclinical randomized controlled multicenter trial (pRCT): anti-CD49d treatment for acute brain ischemia. Sci Transl Med 2015;7:299ra121.
42. Hunniford VT, Grudniewicz A, Fergusson DA, Montroy J, Grigor E, Lansdell C, et al. A systematic assessment of preclinical multilaboratory studies and a comparison to single laboratory studies. Elife 2023;12:e76300.
43. Lin S, Ramadeen A, Sundermann ML, et al. Establishing a multicenter, preclinical consortium in resuscitation: a pilot experimental trial evaluating epinephrine in cardiac arrest. Resuscitation 2022;175:57–63.
44. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Method 2014;14:43.
45. Olai H, Thornéus G, Watson H, et al. Meta-analysis of targeted temperature management in animal models of cardiac arrest. Intensive Care Med Exp 2020;8:3 -.
46. Aagaard R, Granfeldt A, Botker MT, Mygind-Klausen T, Kirkegaard H, Lofgren B. The right ventricle is dilated during resuscitation from cardiac arrest caused by hypovolemia: a porcine ultrasound study. Crit Care Med 2017.
47. Aagaard R, Caap P, Hansson NC, Botker MT, Granfeldt A, Lofgren B. Detection of pulmonary embolism during cardiac arrest-ultrasonographic findings should be interpreted with caution. Crit Care Med 2017.
48. Caap P, Aagaard R, Sloth E, Lofgren B, Granfeldt A. Reduced right ventricular diameter during cardiac arrest caused by tension pneumothorax - a porcine ultrasound study. Acta Anaesthesiol Scand 2017;61:813–23.
49. Sodium Bicarbonate and Calcium Chloride for the Treatment of Hyperkalemia-Induced Cardiac Arrest: A Randomized, Blinded, Placebo-Controlled Animal Study.Eggertsen MA, Munch Johannsen C, Kovacevic A, Fink Vallentin M, Mørk Vammen L, Andersen LW, Granfeldt A.Crit Care Med. 2023 Nov 3. doi: 10.1097/CCM.0000000000006089. Online ahead of print.
50. National Research Council. Committee for the Update of the Guide for the C, Use of Laboratory A, Institute for Laboratory Animal R. Guide for the care and use of laboratory animals. eighth ed. Washington, D.C: National Academies Press; 2011.
51. Systematic Review Centre for Laboratory Animal Experimentation https://www.syrcle.network/.