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Review

Translation from animal studies of novel pharmacological therapies to clinical trials in cardiac arrest: A systematic review

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Abstract

Background: There is a lack of new promising therapies to improve the dismal outcomes from cardiac arrest. The objectives of this study were: (1) To identify novel pharmacological therapies investigated in experimental animal studies and (2) to identify pharmacological therapies translated from experimental animal studies to clinical trials.

Methods: PubMed was searched to first identify relevant experimental cardiac arrest animal models published within the last 20 years. Based on this, a list of interventions was created and a second search was performed to identify clinical trials testing one of these interventions. Data extraction was performed using standardised data extraction forms.

Results: We identified 415 animal studies testing 190 different pharmacological interventions. The most commonly tested interventions were classified as vasopressors, anaesthetics/gases, or interventions aimed at molecular targets. We found 43 clinical trials testing 26 different interventions identified in the animal studies. Of these, 13 trials reported positive findings and 30 trials reported neutral findings with regards to the primary endpoint. No study showed harm of the intervention. Some interventions tested in human clinical trials, had previously been tested in animal studies without a positive effect on outcomes. A large number of animal studies was performed after publication of a clinical trial.

Conclusion: Numerous different pharmacological interventions have been tested in experimental animal models. Despite this only a limited number of these interventions have advanced to clinical trials, however several of the clinical trials tested interventions that were first tested in experimental animal models.

Keywords: Cardiac arrest, Animal models, Clinical trials, Interventions, Drugs, Review

Introduction

Currently the only drugs recommended as standard for use during cardiac arrest are epinephrine and amiodarone/lidocaine.[1–4] The number of clinical trials investigating interventions during cardiac arrest are outnumbered by studies within other fields of cardiovascular medicine such as ischemic heart disease, stroke and chronic heart failure.[5] This compares unfavourably with the substantial morbidity and mortality associated with cardiac arrest, with cardiac arrest as the

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third leading cause of disability-adjusted life years.[6] In a recent review on drugs during cardiopulmonary resuscitation, only six ongoing clinical trials were identified. Furthermore, out of 48 online registered trials for post-cardiac arrest interventions only 14 included pharmacological agents and several of these are already available in clinical practice.[7,8] This lack of new promising therapies to improve the dismal outcomes from cardiac arrest illustrates a serious concern within the field of cardiac arrest.

A systematic review on novel pharmacological therapies investigated in experimental animal studies could inform researchers on new promising pharmacological interventions and on interventions transferred from the animal laboratory to the clinical setting.

The aim of this systematic review was to identify novel pharmacological therapies investigated in experimental animal studies and to identify the number of therapies translated from experimental animal studies to clinical trials.

Methods

Overview

The objective of this paper was twofold: (1) To identify novel pharmacological therapies investigated in experimental animal studies and (2) to identify pharmacological therapies translated from experimental animal studies to human clinical trials. We first performed a search to identify experimental cardiac arrest animal models. Based on this, a list of interventions was created and a second search was performed to identify clinical trials testing one of these interventions.

The review was not registered as it did not compare specific interventional strategies and no detailed review protocol existed. However, the eligibility criteria, search strategies, and a detailed data extraction protocol were created prior to performing the search.

Eligibility criteria

Experimental cardiac arrest animal models

An experimental cardiac arrest animal model was defined as intentional induction of cardiac arrest with subsequent cardiopulmonary resuscitation including manual/mechanical chest compressions or extracorporeal cardiopulmonary resuscitation.[9] Only in vivo studies performed in mammals were included. Pharmacological interventions were defined as a drug administered intra- or post-cardiac arrest to obtain a specific effect. Combinations of pharmacological interventions were also included. Fluids were not considered a pharmacological intervention. The pharmacological intervention had to be compared to a control group (no-treatment, placebo or standard treatment of adrenaline or amiodarone/lidocaine). We excluded cardiac arrest animal models where the cardiac arrest was induced by injection of a pharmacological agent, such as a tricyclic anti-depressant or local anaesthetic (lidocaine, bupivacaine, ropivacaine etc.). However, an exception to this exclusion criterion was cardiac arrest asphyxia models where a muscle relaxant was used, which were included in the review. It was a priori decided not to include studies with adrenaline, lidocaine and amiodarone as interventions, as these are recommended by guidelines and regarded as standard therapy.[10]

Clinical trials

A clinical interventional trial was defined as a randomised trial assessing the intervention of interest in adults with cardiac arrest in any setting (in-hospital or out-of-hospital). Adults were defined as $\geq$18 years (or as defined in individual studies). All types of randomised trials were included. This included quasi-randomised trials (e.g. assignment based on day of the week) as well as cluster-randomised trials.

Information source and search strategy

Experimental animal studies

To identify experimental animal studies, PubMed was searched from 24.02.2000 to 24.02.2020. We only searched PubMed as the gain from including other databases was expected to be low based on our experiences from previous systematic reviews of cardiac arrest interventions.[1,11,12] The first part of the search contained keywords relevant to cardiac arrest, while the second part included relevant types of animals as previously described.[9] The full search strategy is provided in the Supplemental material.

Clinical trials

To identify clinical trials testing the identified pharmacological interventions, we searched PubMed on 11.06.2020. The first part of the search contained keywords relevant to cardiac arrest as previously used.[12] The second part identified randomised clinical trials using the Cochrane sensitivity- and precision-maximising search strategy for identification of randomised clinical trials.[13] The third part contained the identified pharmacological interventions listed in the Supplement material. The search was performed for each intervention category separately. The full search strategy is provided in the Supplemental material.

For both searches, using pre-defined screening criteria, pairs of two reviewers, independently screened all titles and abstracts. The reviewers were blinded to authors and journal titles during the screening stage. Any disagreements regarding inclusion or exclusion were resolved via discussion between the reviewers and with a third reviewer as needed. The same reviewers then reviewed the full-text articles of all potentially relevant publications passing the first level of screening. Any disagreement regarding eligibility was resolved via discussion until consensus was reached. The Kappa-value for inter-observer variance was calculated.

Data collection

Reviewers, using a pre-defined standardised data extraction form, extracted data from individual studies. For evaluation of outcomes in the experimental animal studies we used the following definitions: a) Clinically relevant outcomes included return of spontaneous circulation, survival and survival with a favorable neurological outcome, b) neurological outcomes included cerebral outcomes based on MRI, CT, histology, blood markers, microdialysis, near-infrared spectroscopy, electrophysiology etc., c) cardiovascular outcomes included cardiac output, haemodynamics, blood markers, echocardiography, MRI, cardiac histology, and d) other outcomes include respiratory outcomes, renal outcomes, other blood markers etc.

Statistical analysis

Categorical variables are presented as counts (frequencies) and continuous variables as mean with standard deviation (SD), while non-normally distributed continuous values are presented as median and interquartile range (IQR). Data analyses were performed with Stata 14.0 (StataCorp LP, College Station, TX, USA).

Results

Study selection

Experimental animal studies

A total of 6107 unique records were identified. After review of abstracts, 5658 records were excluded (Kappa = 0.79). Following full-text review, 34 articles were excluded (kappa = 0.66). Reasons for exclusion are listed in Fig. 1. Several of the included studies tested more than one intervention, therefore, a total of 415 studies testing 439 interventions were included. These were published in 110 different journals with an increasing number of studies published over time (Fig. S1, Supplement material)

Clinical trials

A total of 838 unique records were identified (Fig. 2). Following review of abstracts, 51 articles were included for full-text review. Of these 48 were included.

Study characteristics

Experimental animal studies

The most commonly used animal species were rats and pigs with electric pacing and asphyxia as the most common methods of inducing cardiac arrest (Table 1). A total of 190 different interventions were identified with the most commonly tested interventions classified as vasopressors, anaesthetics/gases, or interventions aimed at specific molecular targets (Table S1, Supplement material). The average no-flow period was 8.0 (SD 4.6) minutes while the average time to from cardiac arrest to drug administration was 9.0 (SD 4.9) minutes. For clinically relevant outcomes 42% reported no effect while 37% reported that the intervention improved survival. The majority of studies did not report on neurological outcomes, but for those who did, the majority reported an improvement (Table 1). Out of 190 different interventions, 120 interventions were only tested once. In contrast, 12 interventions were tested in more than five studies with 40 studies testing the effects of vasopressin. 15% of the survival studies applied targeted temperature management with median duration of 4 h (IQR 2–12). For details see the Supplemental material.

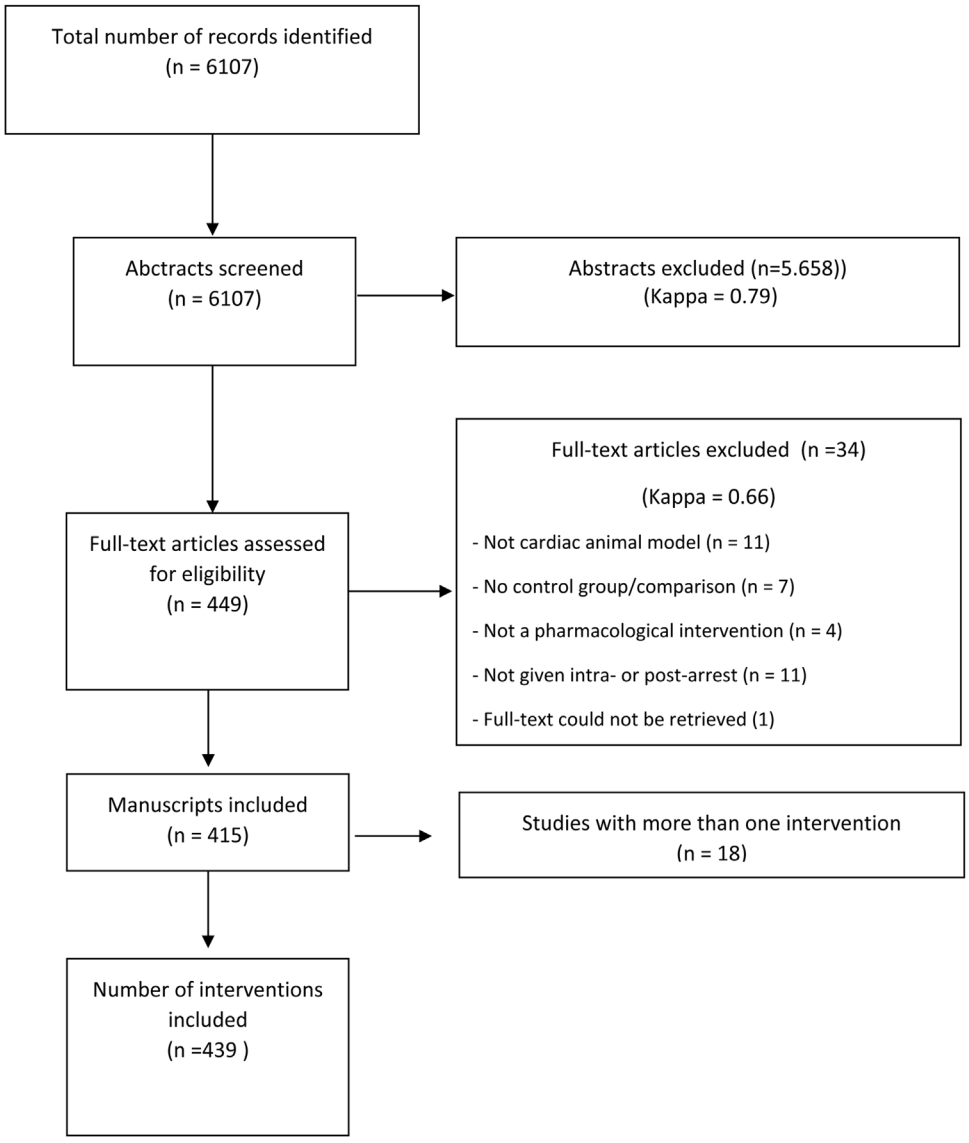

Fig. 1 – PRISMA diagram.
Diagram illustrating the flow of articles throughout the selection procedures of experimental animal studies.

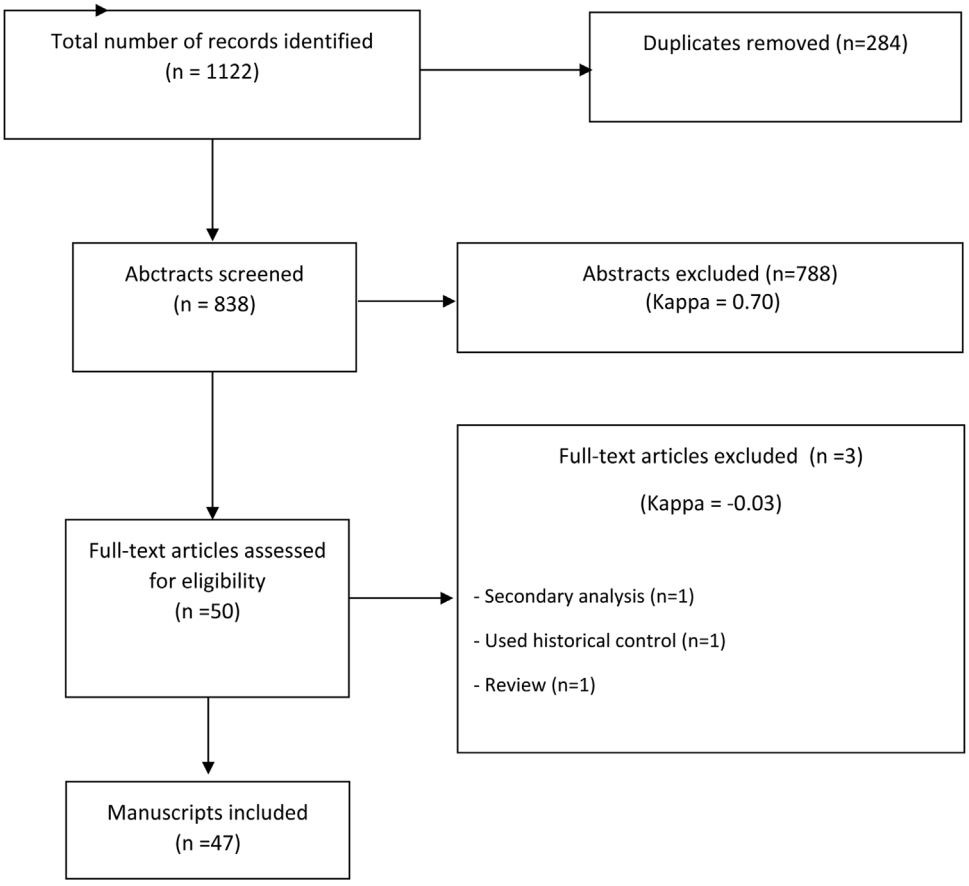

Fig. 2 – PRISMA diagram.
Diagram illustrating the flow of articles throughout the selection procedures of clinical studies.

Clinical trials

The 48 clinical trials included five published trial protocols and tested 26 different interventions (Table 2/Table S2). When evaluating the 29 trials published after 2000, 18 different interventions were tested. Out of the 43 published trials, 13 trials reported positive findings and 30 trials reported neutral findings with regards to the primary endpoint. No trials reported worse outcomes with the intervention being tested. The majority of trials included patients with out-of-hospital cardiac (OHCA) (n = 33) while few studies included patients with in-hospital-cardiac arrest (IHCA) (n = 5) or both OHCA and IHCA (n = 5). Out of the 30 most tested interventions in experimental animal studies, only 9 (30%) of the interventions had been tested or was in the process of being tested in a human clinical trial (Table 3). Some interventions tested in human clinical trials, had previously been tested in animal studies without a positive effect on outcomes. A large number of animal studies was performed after publication of a clinical trial.

Discussion

In the current study, we identified 415 experimental animal studies testing 190 different pharmacological interventions published within the last 20 years. The majority of the interventions were only tested once. When searching for human clinical trials testing one of the 190 different interventions, we identified 43 trials testing 26 different interventions. Some of these intervention had previously been tested in animal studies without a positive effect on outcomes, while a large number of animal studies was performed after publication of a clinical trial.

Survival from cardiac arrest has increased over the last decades, which primarily has been attributed to an increase in bystander interventions such as bystander CPR and use of automated external defibrillators (AED).[14–17] However, the increase in bystander interventions and survival may have reached a plateau.[16–18] Although strategies to increase survival will likely include additional strategies to increase layperson involvement, new interventions and approaches to patients with cardiac arrest are also needed to further improve outcomes.[19] Over the years there have been few changes in the recommended drugs during cardiopulmonary resuscitation. Adrenaline has been included in resuscitation guidelines since the 1960s while amiodarone was included in the 2000 guidelines with further emphasis in the 2005 guidelines.[20,21] Currently there are limited data and ongoing trials to support the inclusion of new intra-cardiac arrest into the resuscitation guidelines, with only six ongoing clinical trials of drugs during adult cardiopulmonary resuscitation.[8] In that context, it is encouraging that 190 different interventions have been tested in experimental animal models and that the number has been increasing over the years, as experimental animal studies are the breeding ground for potential discoveries and new interventions.

Cardiac arrest researchers have demonstrated that large randomised trials can be performed with regards to both intra-arrest

Table 1 – Experimental animal study characteristics.

	Number[a] (%)
Animal species	
Mouse	28 (6)
Rat	203 (46)
Rabbit	15 (4)
Canine (dog)	12 (3)
Pig	181 (41)
Cardiac arrest model	
Electric pacing	253 (57)
Asphyxia	118 (27)
Potassium	35 (8)
Myocardial infarction	5 (1)
Combination	20 (5)
Other[b]	6 (1)
Not reported[c]	2 (1)
Intervention category	
Anesthetics/gases	56 (13)
Anti-arrhythmic agents	25 (6)
Anti-inflammatory	36 (8)
Anti-oxidants	9 (2)
Buffers	4 (1)
Coagulation	7 (1)
Combination therapy	24 (5)
Enzymes/proteases	3 (1)
Herbs/plants	23 (5)
Hormones	22 (5)
Metabolic	12 (3)
Mitochondria	19 (4)
Molecules/molecular targets	47 (11)
Nitrite /bitric oxide/ sodium nitroprusside	20 (4)
Peptides	13 (3)
Pharmacological hypothermia	16 (4)
Vasodilators/inodilators	20 (4)
Vasopressors	74 (17)
Vitamins	5 (1)
Other	4 (1)
Route of administration	
Intravenous	324(74)
Intra-peritoneal	31 (7)
Intramuscular/subcutaneously/Intraosseous	7 (2)
Inhalation	37 (8)
Oral	4 (1)
Intraventricular brain injection	9 (2)
Other[d]	14 (3)
Not reported	13 (3)
Timing of invention	
Intra-cardiac arrest	207 (47)
Post-cardiac arrest	192 (44)
Intra- and post-cardiac arrest	40 (9)
Acute study/survival study[e]	
Acute study	186 (42)
Survival study	253(58)
Clinical relevant outcomes	
Improve	162 (37)
Worse	8 (2)
No effect	184 (42)
Conflicting findings	4 (1)
Not reported	81 (18)
Neurological outcomes	
Improve	163 (37)
Worse	5 (1)
No effect	66 (15)
Conflicting findings	7 (2)
Not reported	198 (45)
Cardiovascular outcomes	
Improve	142 (32)
Worse	13 (3)
No effect	151 (34)
Conflicting findings	11 (3)
Not reported	122 (28)
Other outcomes	
Improve	65 (15)
Worse	1 (0)
No effect	27 (6)
Conflicting findings	0 (0)
Not reported	346 (80)

[a] The numbers are based on the total number of interventions, which exceeds the number of studies.
[b] Pulmonary embolism, major vessel occlusion.
[c] Refers to previous publications.
[d] Includes aortic flush, intra-arterial, combinations.
[e] Acute study — animals are never awakened from anaesthesia, Survival — animals are awakened from anaesthesia.

and post-cardiac arrest intervention.[2,3,22] With regards to intra-cardiac arrest pharmacological interventions, studies are often performed on OHCA patients where the time to drug delivery is approximately 20 min after the onset of cardiac arrest. This is very different from experimental studies where the average time from cardiac arrest to drug administration is 9 min and where the protective effect is often lost if treatment is delayed.[9,23] This lack of experimental animal studies to recapitulate the severity and characteristics of human clinical cardiac arrest illustrates a continuous concern.[9,24] This is also illustrated by the low number of survival studies applying controlled temperature management. In contrast, few studies have been performed on patients with IHCA where the time to drug delivery is considerably shorter.[25,26] The IHCA population may therefore be a more suitable population for testing new promising interventions. Examples of interventional trials in the IHCA population are the two trials testing vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest.[27,28] Both studies reported promising improvements in survival and survival with a good neurological outcome. Although the studies were not directly based on experimental animal studies testing the specific combination of vasopressin and corticosteroids, the idea of adding vasopressin to adrenalin was based on an experimental animal study.[29]

Examples of interventions that were successfully tested in first experimental animal studies and brought into clinical trials includes erythropoietin, Shen Fu, xenon, and nitrite.[30–34] These interventions are characterised by a number of animal studies demonstrating an improvement in outcomes preceding the clinical trials, although a number of animal studies also reported no beneficial effect. The clinical trials of erythropoietin and nitrite reported neutral results, while

Table 2 – Clinical trials testing interventions of interest after year 2000.

First author, year	Intervention category	Intervention	Number of animal studies total	Number of animal studies prior[a]	Patient population	Sample size	Comparator	Primary outcome	Main result
Mader 2003[58]	Other	Aminophylline	1	0	OHCA	111	Placebo	Return of spontaneous circulation	Neutral
Abu-Laban 2006[59]	Other	Aminophylline	1	1	OHCA	971	Placebo	Return of spontaneous circulation	Neutral
Argaud 2016[30]	Mitochrondria	Cyclosporine	7	0	OHCA	794	Standard care	Sequetial Organ Failure Assessment (SOFA) score	Neutral
Cariou 2016[60]	Hormones	Erythropoietin	9	4	OHCA	476	Standard care	Cerebral performance category score 1 at 60 days	Neutral
Wiberg 2016[37]	Hormones	Glucagon-like-peptide-1	2	2	OHCA	120	Placebo	Feasibility and Neuron Specific Enolase Area under the curva after 72 h	Neutral
Tamura 2017[61]	Anesthetics/gases	Hydrogen	8	6	OHCA	360	Placebo	Favorable 90-day neurological outcome	Protocol[b]
Bjelland 2012[38]	Anesthetics/gases	Midazolam and fentanyl versus propofol and remifentanil	1	0	Both	60	Other drug	Time from discontinuation of infusions to extubation or decision not to extubate	Positive
Yoshioka 2006[62]	Antiarrhythmic agents	Nifekalant	2	0	Both	91	Other drug	Not defined	Positive[c]
Amino 2010[63]	Antiarrhythmic agents	Nifekalant	2	0	OHCA	30	Other drug	Not defined	Neutral
Zhang 2017[32]	Herbs/plants	Shen Fu	15	3	IHCA	978	Standard care	28 day mortality	Positive
Shao 2020[31]	Herbs/plants	Shen Fu	15	6	OHCA	1201	Placebo	survival to hospital admission	Positive
Vukmir 2006[64]	Buffers	Sodium bicarbonate	1	0	OHCA	792	Placebo	Return of spontaneous circulation and presenting to the emergency department with a pulse	Neutral
Ahn 2018[65]	Buffers	Sodium bicarbonate	1	1	OHCA	50	Placebo	Change in acidosis	Positive
Dezfulian 2018[33]	Nitrite/Nitric oxide/SNP	Sodium nitrite high and low dose	4	1	OHCA	11	Placebo	Feasibilty and hypotension as an adverse event	Neutral

(continued on next page)

Table 2 *(continued)*

First author, year	Intervention category	Intervention	Number of animal studies total	Number of animal studies prior[a]	Patient population	Sample size	Comparator	Primary outcome	Main result
Abu-Laban 2002[66]	Coagulation	Tissue plasminogen activator	1	0	Both	233	Placebo	Survival to hospital discharge	Neutral
Fatovich 2004[67]	Coagulation	Trombolysis/ Tenecteplase	1	0	OHCA	35	Placebo	Return of spontaneous circulation	Positive
Böttiger 2008[68]	Coagulation	Trombolysis/ Tenecteplase	1	0	OHCA	1050	Placebo	30-day survival	Neutral
Liu 2017[69]	Anti-inflammatory	Ulinastatin + continuous renal replacement therapy	9	6	IHCA	70	Standard care	Multiple biomarkers	Positive
Stiell 2001[70]	Vasopressors	Vasopressin	40	0	IHCA	200	Epinephrine	1 h survival	Neutral
Wenzel 2004[40]	Vasopressors	Vasopressin	40	0	IHCA	1186	Epinephrine	Survival to hospital admission	Neutral[d]
Mukoyama 2009[71]	Vasopressors	Vasopressin	40	11	OHCA	336	Epinephrine	Survival to hospital discharge and favorable neurological outcome with hospital discharge	Neutral
Ong 2012[72]	Vasopressors	Vasopressin	40	24	OHCA	727	Epinephrine	Survival to hospital discharge	Neutral
Mentzelopoulos 2009[27]	Combination therapy	Vasopressin + corticosteroids[e]	1	0	IHCA	100	Placebo	Return of spontaneous circulation and survival to hospital discharge	Positive
Mentzelopoulos 2013[28]	Combination therapy	Vasopressin + corticosteroids[e]	1	0	IHCA	300	Placebo	Return of spontaneous circulation and survival to hospital discharge with a favorable neurological outcome	Positive
Callaway 2006[73]	Vasopressors	Vasopressin + epinephrine	5	2	OHCA	325	Epinephrine	Return of spontaneous circulation	Neutral
Gueugniaud 2008[39]	Vasopressors	Vasopressin + epinephrine	5	2	OHCA	2894	Epinephrine	Survival to hospital admission	Neutral
Ghafourian 2015[74]	Vasopressors	Vasopressin + epinephrine	5	5	OHCA	100	Epinephrine	S100b	Neutral
Ducros 2011[75]	Combination therapy	Vasopressin + epinephrine or Vasopressin + epinephrine + nitroglycerin	2	0	OHCA	44	Epinephrine	Diastolic blood pressure during CPR	Neutral

Table 2 (continued)

First author, year	Intervention category	Intervention	Number of animal studies total	Number of animal studies prior[a]	Patient population	Sample size	Comparator	Primary outcome	Main result
Arola 2013[76]	Anesthetics/ gases	Xenon	4	3	OHCA	33	No comparator	Feasibility and cardiac safety	Neutral
Laitio 2016[34]	Anesthetics/ gases	Xenon	4	3	OHCA	110	Standard care	Severity of ischemic whitematter brain injury in MRI	Positive

[a] Number of animal studies prior to start of patient inclusion. Note that animals studies published prior to 24.02.2000 were not included.
[b] Only published as a trial protocol.
[c] Positive effect on defibrillation rate.
[d] Significant effect in patients with asystole.
[e] Animal study used terlipressin.

the clinical trials of Shen Fu and xenon demonstrated promising results. For xenon, this has led to a larger clinical trial (Xenon by Inhalation for Post Out of Hospital Cardiac Arrest Syndrome [XePOHCAS]). In contrast, a clinical trial of Glucagon-like peptide-1 demonstrating neutral results was preceded by experimental animals studies with no effect on the investigated clinical relevant outomes.[35–37] It is also important to consider that not all clinical trials need to be preceded by experimental animal studies. The study by Bjelland et al.[38] tested propofol and remifentanil versus midazolam and fentanyl for sedation during therapeutic hypothermia after cardiac arrest. As the trial included already clinically approved drugs and a clinically relevant endpoint of time to extubation, preceding animal studies are less relevant. Likewise, interventions demonstrating protective properties in corresponding diseases such a myocardial ischemia-reperfusion injury and stroke may be translated directly to cardiac arrest patients. In contrast, the effects of some interventions may be explored in too many experimental studies. From 2000 to 2017, 41 animal studies investigated the effects of vasopressin. Given that large randomised trials in humans have shown no improvements in outcomes with vasopressin, it is questionable whether additional animal studies will be beneficial.[39,40]

It is difficult to pinpointwhat determines whether an intervention is transferred from the animal laboratory to the clinical setting. For instance, the intervention most commonly tested in animal studies, besides vasopressin and Shen Fu, is sodium hydrogen exchange inhibitors, with some studies, including large animal studies, demonstrating protective properties.[41,42] Yet no clinical studies have tested the effects of sodium hydrogen exchange inhibitors in patients with cardiac arrest. Methylene blue is another example with four out of five large animal studies demonstrating neuroprotective effects and no clinical studies testing methylene blue in patients with cardiac arrest.[43–47] In a highly competitive research environment, research groups often specialise within a specific field such as experimental animals studies, observational studies, or clinical trials as each area requires a different set of skills. With the ongoing emergence of new journals dedicated to experimental research, promising findings from animal studies may lack reach and promising findings in experimental animal studies may not generate the necessary attention for clinical researchers. Furthermore, the “reproducibility crisis” within experimental research has led to a scepticism towards basic science and experimental animal studies, which may limit enthusiasm from clinical researchers.[48]

To address this scepticism meticulous testing of new interventions in multiple animal models and laboratories before clinical translation could be an answer. Inspiration for this can be found within fields such as epilepsy, myocardial infarction, traumatic brain injury and stroke.[49–52] This includes the development of programs or consortiums that screens potential new drugs in different animal models displaying different aspects of the disease of interest. It also include a standardization of endpoints that recapitulate human clinical features and minimize bias across sites.[50,51]

Two promising interventions identified during this review is hydrogen and glibenclamide. Hydrogen, an effective antioxidant, and glibenclamide, a sulfonylurea receptor 1-transient receptor potential M4 inhibitor, demonstrated an improvement in clinically relevant outcomes in all included studies. Furthermore, glibenclamide is already used clinically for the treatment of type 2 diabetes, while hydrogen has been tested in clinical trials.[53,54–57] However, they have only been tested in small animal models why studies in large animal models is needed. We hope this review and list of potential promising

Table 3 – The experimental pharmacological interventions with most studies published.

Intervention	Intervention category	Number of animal studies total	Improvement in Clinical relevant outcomes	Improvement in Neurological outcomes	Improvement in Cardiovascular outcomes	Improvement in Other outcomes	Number of clinical studies total
Vasopressin	Vasopressors	40	20/36 (56 %)	3/7 (43 %)	17/32 (53 %)	4/5 (80 %)	4
Shen Fu	Herbs/plants	15	1/10 (10 %)	2/5 (40 %)	10/13 (77 %)	7/7 (100 %)	2
Sodium hydrogen exchange inhibitors	Molecules/molecular targets	14	2/12 (17 %)	1/4 (25 %)	6/12 (50 %)	2/4 (50 %)	0
Beta-blockers	Antiarrhythmic agents	11	4/10 (40 %)	1/1 (100 %)	6/11 (55 %)	2/2 (100 %)	0
Erythropoietin	Hormones	9	4/8 (50 %)	2/2 (100 %)	2/8 (25 %)	3/4 (75 %)	1
Ulinastatin trypsin inhibitor	Anti-inflammatory	9	4/8 (44 %)	5/6 (83 %)	3/5 (60 %)	4/4 (100 %)	2
Hydrogen	Anesthetics/gases	8	8/8 (100 %)	7/8 (88 %)	3/6 (50 %)	1/3 (33 %)	0
Sevoflurane	Anesthetics/gases	8	1/7 (14 %)	1/2 (50 %)	3/7 (43 %)	2/4 (50 %)	0
Sodium nitroprusside	Nitrite/Nitric oxide/Sodium nitroprusside	7	6/7 (86 %)	2/3 (67 %)	5/7 (71 %)	1/1 (100 %)	0
Levosimendan	Vasodilators/Inodilators	7	3/6 (50 %)	3/3 (100 %)	5/7 (71 %)	2/2 (100 %)	0
Cyclosporine	Mitochrondria	7	3/6 (50 %)	3/4 (75 %)	4/6 (67 %)	3/4 (100 %)	1
Argon	Anesthetics/gases	6	1/4 (25 %)	4/6 (67 %)	0/4 (0%)	0/2 (0%)	0
Glibenclamide	Metabolic	5	4/4 (100 %)	5/5 (100 %)	0/2 (0%)		0
Carbon monoxide	Anesthetics/gases	5	2/2 (100 %)	2/2 (100 %)	2/2 (100 %)	1/1 (100 %)	0
Hydrogen sulfide	Anesthetics/gases	5	4/5 (80 %)	5/5 (100 %)		1/1 (100 %)	1[a]
Isoflurane	Anesthetics/gases	5	2/5 (40 %)	3/4 (75)	0/5 (0%)		0
Sodium sulfide	Anesthetics/gases	5	2/5 (40 %)	3/5 (60 %)	1/4 (25 %)		0
Minocycline (tetracycline)	Anti-inflammatory	5	0/3 (0%)	3/5 (60 %)	0/2 (0%)		0
Estradiol	Hormones	5	1/4 (25 %)	1/3 (33 %)	0/2 (0%)	1/1 (100 %)	0
Nitric oxide	Nitrite/Nitric oxide/Sodium nitroprusside	5	4/5 (80 %)	3/4 (75 %)	2/4 (50 %)	1/2 (50 %)	0
Endothelin-1	Vasopressors	5	0/3 (0%)	0/1 (0%)	1/5 (20 %)		0
Methylene blue	Vasopressors	5	0/3 (0%)	4/4 (100 %)	0/3 (0%)	1/2 (50 %)	0
Naloxone	Vasopressors	5	2/5 (40 %)	0/1 (0%)	0/5 (0%)		0
Dobutamine	Vasodilators/Inodilators	5	1/1 (100 %)		5/5 (100 %)	0/1 (0%)	
Vasopressin + adrenaline	Vasopressors	5	1/5 (20 %)	1/2 (50 %)	1/4 (25 %)	1/2 (50 %)	3
Xenon	Anesthetics/gases	4	2/4 (50 %)	2/3 (66.7 %)	0/4 (0%)		2
Anti-tumor necrosis factor-α Etanercept or Infliximab	Anti-inflammatory	4	1/2 (50 %)		3/4 (75 %)		0
Pyruvate	Metabolic	4	0/2 (0%)	2/2 (100 %)	0/3 (0%)		0
Nitrite	Nitrite/Nitric oxide/Sodium nitroprusside	4	1/4 (25 %)	2/3 (67 %)	2/4 (50 %)		1
Cannabinoid receptor agonist WIN55, 212−2	Pharmacological hypothermia	4	2/3 (67 %)	1/2 (50 %)	3/4 (75 %)		0
Alpha-methylnoradrenaline/α-methylnorepinephrine/alfa-2 adrenoceptor agonist	Vasopressors	4	2/3 (67 %)		2/4 (50 %)		0

Percentage of studies with an improvement in reported outcomes. If no outcomes reported field is left blank.
[a] Only published as a trial protocol.

interventions will bring focus to this area and encourage cardiac arrest researchers within different disciplines to collaborate.

Limitations

Dividing the different interventions into categories have some degree of subjectivity as some interventions could fit into several categories. Similarly, when assessing the effect of the intervention on outcomes this was broadly categorised in order to provide some overview. Although we tried to standardise the categorisation and generally adapted the authors' conclusions, any categorisation comes with some degree of subjectivity. Although the searches and study selection were performed systematically we cannot rule out that potential animal studies or clinical trials were missed. The review did not include studies with adrenaline, lidocaine and amiodarone as interventions. Hence, it is a limitation that the review did not include studies testing the optimal dosing regimens ((e.g. dosing, time between dosing, infusion)) of these drugs. Furthermore, the timespan from initiation of a clinical trial to publication is often several years, why we cannot rule out that ongoing trials were missed. However, published trial protocols were included. In addition, as we excluded trials where the intervention was administered prior to the cardiac

arrest, clinical trials could have been based on an animal study were the intervention was administered pre-cardiac arrest. The Kappa value for full-text review of clinical studies was low and indicating an agreement that is no better than that which would be obtained by chance alone. This is partly due to the low number of articles, as there was only disagreement with regards to the three excluded studies.

Conclusion

Numerous different pharmacological interventions have been tested in experimental animal models. Despite this only a limited number of these interventions have advanced to clinical trials, however several of the clinical trials tested interventions that were first tested in experimental animal models.

Author contribution

All authors have contributed to all the of following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Conflict of interest

None.

CRediT authorship contribution statement

Peter Carøe Lind: Data curation, Investigation, Writing - review & editing. **Cecilie Munch Johannsen:** Data curation, Investigation, Writing - review & editing. **Lauge Vammen:** Data curation, Investigation, Writing - review & editing. **Andreas Magnussen:** Data curation, Investigation, Writing - review & editing. **Lars W. Andersen:** Conceptualization, Investigation, Methodology, Supervision, Writing - review & editing. **Asger Granfeldt:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, https://doi.org/10.1016/j.resuscitation.2020.10.028.

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