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Review article

Contemporary animal models of cardiac arrest: A systematic review☆

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ABSTRACT

Aim of the study: Animal models are widely used in cardiac arrest research. This systematic review aimed to provide an overview of contemporary animal models of cardiac arrest.
Methods: Using a comprehensive research strategy, we searched PubMed and EMBASE from March 8, 2011 to March 8, 2016 for cardiac arrest animal models. Two investigators reviewed titles and abstracts for full text inclusions from which data were extracted according to pre-defined definitions.
Results: Search criteria yielded 1741 unique titles and abstracts of which 490 full articles were included. The most common animals used were pigs (52%) followed by rats (35%) and mice (6%). Studies favored males (52%) over females (16%); 17% of studies included both sexes, while 14% omitted to report on sex. The most common methods for induction of cardiac arrest were either electrically-induced ventricular fibrillation (54%), asphyxia (25%), or potassium (8%). The median no-flow time was 8 min (quartiles: 5, 8, range: 0–37 min). The majority of studies used adrenaline during resuscitation (64%), while bicarbonate (17%), vasopressin (8%) and other drugs were used less prevalently. In 53% of the studies, the post-cardiac arrest observation time was ≥24 h. Neurological function was an outcome in 48% of studies while 43% included assessment of a cardiac outcome.
Conclusions: Multiple animal models of cardiac arrest exist. The great heterogeneity of these models along with great variability in definitions and reporting make comparisons between studies difficult. There is a need for standardization of animal cardiac arrest research and reporting.

Introduction

Animal models of cardiac arrest constitute a cornerstone in resuscitation research as an instrument to address the poor outcomes following cardiac arrest.[1] Through their ability to create well-defined conditions and the performance of measurements not possible in humans, animal models of cardiac arrest provide a unique opportunity to advance the science by elucidating underlying pathophysiological mechanisms and by developing and testing of new therapies.

Although the ultimate goal of animal studies is to reflect the clinical scenario, most models fail to reflect human critical illness making it difficult to directly translate the results obtained from animal studies into a human clinical setting.[2] These limitations in animal model design and reporting are by experts considered as a root cause for the failure of neuroprotective strategies with preclinical promise to translate to humans.[3–8] Furthermore, our knowledge regarding the pathophysiology of cardiac arrest is derived from multiple different animal models of varying clinical relevance. Thus, it is important to review the existing reporting standards and methods used within recently used different models of cardiac arrest. With this objective, we performed a systematic review to give a detailed overview on contemporary animal models of cardiac arrest.

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Methods

Definitions and inclusion/exclusion criteria

The systematic review was performed in accordance with the PRISMA guidelines (Supplemental material).[9] The review was not registered and no detailed review protocol existed, however the definition of a cardiac arrest animal model, search strategies, and a detailed data extraction protocol was created prior to performing the search.

A 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. Studies of all types (diagnostic, prognostic, interventional, or pathophysiological) were included.

Only in vivo studies performed in mammals were included. Since this review focuses on contemporary animal models, we only included studies from the last five years. The search was restricted to English studies. Letters, commentaries, editorials, case reports, reviews and solitary abstracts were excluded.

Search strategies and data extraction

We searched PubMed and EMBASE from March 8, 2011 to March 8, 2016. The first part of the search strategy contained keywords relevant to cardiac arrest, while the second part of the search strategy included all relevant types of animals utilizing a modification of the search strategy suggested by Hooijmans et al.[10] The full search strategy is provided in the Supplemental material.

Two reviewers independently screened titles and abstracts for relevant articles. Following initial screening, full text articles were then reviewed and, if deemed appropriate for inclusion, data were extracted according to pre-defined definitions (see Supplemental material). Initially, data were extracted from 10 full text articles and compared between reviewers to ensure uniform data extraction. As our primary interests were the methodology of the cardiac arrest models and not any potential intervention tested, the data from the control group were included when the study involved more than one group. If the control group consisted of multiple groups, i.e. animals sacrificed at multiple time points, data from the group with the longest observation period were extracted. We only included data that were presented in the paper itself, i.e. we did not consider data provided in References.

Statistical approach

Descriptive statistics were used to characterize included studies. Kappa statistic was used to assess inter-rater agreement between the two reviewers. Groups were compared using Chi-squared test for categorical variables and the Wilcoxon Rank Sum test was used for continuous variables. Statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Articles included and animal characteristics

The two reviewers assessed 1741 unique titles and abstracts; this yielded full review of 511 articles of which 490 full articles were included (see Fig. 1). A full list of the 490 studies are provided in the Supplemental material. The 490 articles were published in 154 different journals. Journals publishing the highest number of cardiac arrest animal studies included Resuscitation (101 articles [21%]), The American Journal of Emergency Medicine (38 articles [8%]), and Critical Care Medicine (34 articles [7%]) (see Table 2 in the Supplemental material).

Table 1
Animal characteristics. Q8

Variable	All studies (n = 490)
Type of animal—n (%)	
Pig	256 (52)
Rat	171 (35)
Mouse	29 (6)
Rabbit	21 (4)
Canine (dog)	10 (2)
Sheep	2 (<1)
Monkey	1 (<1)
Age—n (%)	
Adult	443 (90)
Pediatric	43 (9)
Aged	2 (<1)
More than one age group	2 (<1)
Sex—n (%)	
Male	252 (52)
Female	79 (16)
Both	84 (17)
Not reported	70 (14)
Morbidity—n (%)	
Normal animals	475 (97)
Genetically modified	10 (2)
Co-morbid condition	5 (1)
Weight (g)—median (quartiles)[a]	
Pig	30,000 (20,300, 35,000)
Rat	350 (300, 445)
Mouse	23 (23, 26)
Rabbit	2750 (2320, 3000)
Number of animals—median (quartiles)[b]	
Pig	9 (7, 12)
Rat	10 (6, 15)
Mouse	11 (8, 14)
Rabbit	12 (10,15)

[a] Data not reported for 9 pig, 12 rat, 8 mouse, and 2 rabbit studies.
[b] Data not reported for 1 pig, 7 mouse, and 3 rat studies.

The majority of studies compared interventions (311 [63%]) or investigated pathophysiology (134 [27%]). The remaining studies focused on prognostication (13 [3%]), diagnostics (6 [1%]), or a combination of the above (21 [4%]). Only 61 studies (12%) referred to the 1996 Utstein-Style Guidelines for Uniform Reporting of Laboratory CPR Research[11] while 201 studies (41%) provided incomplete methods referring to prior articles for complete methodology. These prior articles were not further assessed.

Characteristics of the animals included in the studies are provided in Table 1. The most common animal type used was pig followed by rat, mouse, and rabbit. Male animals were used three times more often than female animals. About one-fifth of the studies used both female and male animals. Almost all studies used adult animals that were otherwise healthy. The median number of animals used in the control group was 10 (quartiles: 7, 13).

Pre-cardiac arrest characteristics

Table 2 provides pre-cardiac arrest characteristics for all studies as well as stratified by the most commonly used type of animals. The choice of anaesthesia varied substantially according to the type of animal used: with inhalational and intraperitoneal anaesthesia used mostly in rodents as opposed to intravenous anaesthesia used mostly in pigs. The pre-cardiac arrest fraction of inspired oxygen was 21% in most studies. The majority of studies did not report on an abundant number of our pre-defined characteristics (i.e. fasting, anaesthesia turned off, or baseline period).

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