Heart failure supported by veno-arterial extracorporeal membrane oxygenation (ECMO): a systematic review of pre-clinical models

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Abstract

Objectives: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used to treat patients with refractory severe heart failure. Large animal models are developed to help understand physiology and build translational research projects. In order to better understand those experimental models, we conducted a systematic literature review of animal models combining heart failure and VA-ECMO.

Studies selection: A systematic review was performed using Medline via PubMed, EMBASE, and Web of Science, from January 1996 to January 2019. Animal models combining experimental acute heart failure and ECMO were included. Clinical studies, abstracts, and studies not employing VA-ECMO were excluded.

Data extraction: Following variables were extracted, relating to four key features: (1) study design, (2) animals and their peri-experimental care, (3) heart failure models and characteristics, and (4) ECMO characteristics and management.

Results: Nineteen models of heart failure and VA-ECMO were included in this review. All were performed in large animals, the majority (n = 13) in pigs. Acute myocardial infarction (n = 11) with left anterior descending coronary ligation (n = 9) was the commonest mean of inducing heart failure. Most models employed peripheral VA-ECMO (n = 14) with limited reporting.

Conclusion: Among models that combined severe heart failure and VA-ECMO, there is a large heterogeneity in both design and reporting, as well as methods employed for heart failure. There is a need for standardization of reporting and minimum dataset to ensure translational research achieve high-quality standards.

Keywords: Heart failure, Extracorporeal membrane oxygenation, Animal models
**Introduction**

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a therapeutic option for critically ill patients with cardiogenic shock, pulmonary embolism, or septic shock who are refractory to conventional treatments [1–3]. It consists of an extracorporeal life support (ECLS) circuit and a membrane lung with a venous drainage and an arterial return. Advances in technology, miniature ECMO consoles and improved circuit biocompatibility have exponentially increased the use of VA-ECMO over the last decade and helped broaden its indications [4, 5]. To further improve outcomes and reduce complications associated with the use of VA-ECMO, high-quality clinical research is required [6].

Animal models constitute a cornerstone of critical care research, especially in the field of mechanical organ support, as they can provide a basis for understanding physiology and design relevant clinical trials. Although the ultimate goal of animal studies is to reflect the clinical scenario, the variability in methods used sometimes makes it difficult to directly translate the results obtained into clinically valuable therapeutic approaches. Multiple animal models using VA-ECMO have been published over many years; however, a comprehensive comparison between different models, in terms of feasibility and methods, is lacking, causing controversy within the field.

Therefore, we conducted a systematic review to summarize distinctive features of available animal models of heart failure supported by VA-ECMO, and to highlight potential limitations, with the goal of identifying best practices for use in the design of future studies.

**Methods**

This systematic review was performed following PRISMA guidelines [7]. The design was prepared in accordance with the SYRCLE guidelines [8], and the protocol was published on the PROSPERO website (https://www2.le.ac.uk/library/find/databases/p/prospero) under the registration number CRD42018090364.

**Inclusion and exclusion criteria**

Our review covered animal models of heart failure supported by VA-ECMO with no restriction to the publication language. This comprised studies of all types which matched the following PICO approach: (1) population defined as animals with heart failure; (2) intervention defined as animals treated with VA-ECMO; (3) controls defined as animals not treated with VA-ECMO (when the study involved more than one group); and (4) outcomes comprised data reporting quality, characteristics of heart failure, and ECMO support.

Studies using VA-ECMO in the context of cardiac arrest were excluded, as extracorporeal cardiopulmonary resuscitation (ECPR) represents a different clinical scenario and carries its own definition [9].

**Search strategy and data extraction**

We used PubMed, Web of Science, and EMBASE to search for animal models of heart failure on VA-ECMO from January 1st, 1996 to January 1st, 2019. The search contained keywords relevant to cardiac failure and VA extracorporeal membrane
oxygenation, applying pre-published animal filters when relevant [10, 11]. References from identified studies and relevant review articles were also searched for additional eligible citations. The full search strategy is provided in the Supplementary materials.

Two independent reviewers (SH and IR) initially screened articles based on their titles and abstracts. Full-text articles were subsequently independently reviewed (SH and SR) and data were extracted according to a data extraction form available in the Supplementary materials eTable 1. In case of discrepancies, an independent reviewer was consulted (JM). We only included data that were presented in the reviewed paper itself, except when the paper relied on a model described elsewhere by the same authors.

Study outcomes

Quality of reporting

Global quality of data reporting was assessed using the ARRIVE guidelines which provide specific recommendations for methodology and results in animal studies (see Supplementary materials eTables 2 and 3) [12].

To assess the methodology used for acute heart failure models, we compared criteria used by each study with established guidelines or large international trials, adapted to fit with animal practice [13–17]. Although not every study was designed to study cardiogenic shock, specifically, we considered it of matter as it is the clinical situation in which VA-ECMO is mostly used. We thus considered that a study had defined cardiogenic shock adequately if (1) it was consistent with the guidelines in force at the time of the experiment; (2) it used a combination of two criteria present in any guidelines including at least one clinical criterion; or (3) it used one criterion present in any guidelines and successfully induced acute heart failure. When a study failed to meet cardiogenic shock criteria, it was considered as “acute heart failure without cardiogenic shock.”

Heart failure models: characteristics and comparison

The data extraction protocol consisted of the following parameters: type of heart failure induction, methods used to induce heart failure, and criteria used to define cardiogenic shock (as described above) and complications. Details of the definitions used can be found in the Supplementary materials eTable 1.

VA-ECMO support characteristics

Parameters included in the data extraction protocol consisted of the type of console/pump, oxygenator, priming solution, ECMO configuration and access, cannulation technique and size, anticoagulation drug and target. Details of the definitions used can be found in the Supplementary materials eTable 1.

Statistical analysis

Data were analyzed using descriptive statistics and reported as number of occurrences (percentage) or mean ± standard deviation, unless otherwise stated. Given the heterogeneous nature of included studies and taking into account that the aim of the review is to characterize and assess the quality of the models rather than the study outcomes, no attempt was made at meta-analysis.
Results

Study selection and animal characteristics

A total of 349 articles were retrieved through the search from PubMed, Web of Science, and EMBASE. After removing duplicates, 270 studies were screened by titles and abstracts of which 21 full-text articles were reviewed to finally include 19 studies in the systematic review [18–36] (Fig. 1).

The median study population was ten animals per study (from two to 26) and the majority (12/19, 63%) used porcine models [18, 19]. Animal age was missing in nearly half of the studies reviewed, while anesthetic and airway management were only reported in 22% and 17% of studies, respectively (details can be found in the Supplementary materials eTable 4). Housing and husbandry were systematically omitted, and in 12 out of 19 studies, animals’ fasting protocol was not mentioned. Ten studies (53%) had several groups and could thus be qualified as interventional studies (Table 1).

Quality of reporting

Detailed results regarding the concordance of the applied methodology with the ARRIVE checklist can be found in the Supplementary materials eTables 2 and 3.

General quality of reporting was considered mediocre due to the marginal description of materials and methods and to the heterogeneity in the interventions. As for the description of the methods used to develop heart failure, four studies did not report any criteria to define heart failure [20–23]. One study did not present hemodynamic results, rendering it impossible to assess if the cardiogenic shock was achieved during the experiment, or not [24]. Of the remaining 15 studies, ten (66%) used criteria consistent with adequate cardiogenic shock definition and seven (47%) reported enough data to confirm that animals reached cardiogenic shock (the two Esmolol-induced models and...
| Study          | Year | Species | Study type | Animal age\(^a\) | Number | Heart failure model | ECMO configuration                                                                 |
|---------------|------|---------|------------|------------------|--------|---------------------|-------------------------------------------------------------------------------------|
| Sakamoto et al. | 2015 | Dogs    | Other      | Adult            | 21     | Myocardial infarction | ECMO with AMI (n = 13) ECMO without cardiac failure (n = 8)                         |
| Kawashima et al. | 2011 | Dogs    | Physiological | Adult        | 6      | Myocardial infarction | RA-Af                                                                               |
| Yu et al.      | 2008 | Dogs    | Interventional | ND             | 13     | Myocardial infarction | RA-Af Pulsatile ECMO (n = 7) Non-pulsatile ECMO (n = 6)                             |
| Segesser et al. | 2008 | Ox      | Physiological | ND             | 5      | PACing              | Vf and P,p = Â0,Â1                                                                  |
| Møller-Helgestad et al. | 2018 | Pigs    | Interventional | ND             | 14     | Myocardial infarction | ECMO (n = 6) Impella (n = 6)                                                       |
| Ostadal et al. | 2018 | Pigs    | Physiological | 4-5 months     | 16     | Myocardial hypoxia   | ECMO (n = 6) Conventional treatment (n = 6)                                         |
| Simonsen et al. | 2018 | Pigs    | Interventional | 90 days        | 12     | Carbon monoxide poisoning | ECMO (n = 6) Conventional treatment (n = 6)                                         |
| Janak et al.   | 2017 | Pigs    | Physiological | 4-5 months     | 8      | Myocardial infarction | ECMO + normothermia (n = 6) ECMO + hypothermia (n = 6)                             |
| Vanhuyse et al. | 2017 | Pigs    | Interventional | ND             | 12     | Myocardial infarction | ECMO (n = 4) TandemHeart (n = 4)                                                   |
| Esposito et al. | 2016 | Pigs    | Interventional | Adult          | 10     | Myocardial infarction | ECMO (n = 6)                                                        |
| Hala et al.    | 2016 | Pigs    | Physiological | Up to 6 months | 5      | PACing              | ECMO (n = 6) Conventional treatment (n = 6)                                         |
| Itoh et al.    | 2015 | Pigs    | Interventional | ND             | 14     | PACing              | RA-AO Non-pulsatile ECMO (n = 7)                                                   |
| Ostadal et al. | 2015 | Pigs    | Physiological | 4-5 months     | 5      | Myocardial hypoxia   | ECMO (n = 6) Conventional treatment (n = 6)                                         |
| Brehm et al.   | 2014 | Pigs    | Physiological | ND             | 7      | Drug-induced (Esmolol) | ECMO (n = 6) Conventional treatment (n = 6)                                         |
| Kajimoto et al. | 2014 | Pigs    | Interventional | 30-57 days     | 19     | Myocardial infarction | RA-AO ECMO vs IABP (n = 10) ECMO vs PFVAD (n = 10) ECMO vs CFVAD (n = 6) |
| Zhu et al.     | 2014 | Pigs    | Interventional | 4-5 months     | 24     | Myocardial infarction | ECMO (n = 8) Control/sham (n = 8) Drug therapy (n = 8)                              |
| Bartoli et al. | 2013 | Pigs    | Interventional | ND             | 47     | Myocardial infarction | ECMO vs IABP (n = 10) ECMO vs PFVAD (n = 10) ECMO vs CFVAD (n = 6)                 |
| Sauren et al.  | 2007 | Sheep   | Physiological | ND             | 7      | Myocardial infarction | ECMO (n = 6) Conventional treatment (n = 6)                                         |
| Naito et al.   | 2017 | Sheep   | Physiological | Adult          | 6      | Drug-induced (Esmolol) | ECMO (n = 6) Conventional treatment (n = 6)                                         |

*AMI acute myocardial infarction; AF femoral artery; AO aorta; AR right atrium; asc. ascending; CAR carotid artery; CFVAD continuous-flow ventricular assist device; P pulmonary artery; PFVAD pulsatile-flow ventricular assist device; Vf femoral vein; Vf jugular vein

\(^a\)Animal age is written as per original paper statement

\(^b\)Venous canula was first inserted into the right atrium through femoral access (as per peripheral VA-ECMO) and then pushed onto the left pulmonary artery; arterial canula was maintained in the carotid throughout the experiment (as per pediatric ECMO configuration)

\(^c\)Arterial canula was inserted surgically directly into the abdominal aorta through a graft
five models of acute myocardial infarction). The last five studies were considered to have reached acute heart failure but without cardiogenic shock (Table 2).

Heart failure models

**Characteristics of heart failure models**

Heart failure models are presented in Fig. 2 and their characteristics are summarized in Table 3. All models but one [25] described acute heart failure. The majority of studies used an acute myocardial infarction (AMI) model \( (n = 11) \) with left anterior descending (LAD) coronary occlusion, mostly done through ligation. Other models used pacing \( (n = 3) \) [22, 25, 26] to induce ventricular fibrillation (VF), esmolol infusion \( (n = 2) \) [27, 28], myocardial hypoxia \( (n = 2) \) [29, 30], or carbon monoxide poisoning \( (n = 1) \) [31]. The AMI model was systematically complicated with at least two episodes of irreversible VF leading to death, ranging from 9 to 50% of the subjects. This model seemed to display more complications than the others (no statistical analysis could be made because of poor reporting).

**VA-ECMO support characteristics**

Characteristics of VA-ECMO are summarized in Table 4. Most studies \( (17/19) \) employed peripheral or combined cannulation through percutaneous \( (n = 6) \) or a surgical cut-down \( (n = 4) \). However, in nine out of 19 studies, cannulation methods were not described. Cannula size was omitted in four studies and none reported the cannula length. Furthermore, and importantly, arterial tip positioning was only confirmed in three \( [25, 29, 30] \) out of the twelve studies which used peripheral return cannulation. All studies used intravenous infusion of heparin, yet seven of the 19 studies \( (37\%) \) did not report any anticoagulation strategy targets. The combination of ECMO consoles, pumps, and oxygenators across studies was highly diverse. Finally, the priming solution was described only in six studies with wide variation [18, 21, 22, 24, 25, 32].

**Discussion**

In this systematic review, we provided a comprehensive overview of available preclinical models of heart failure supported by VA-ECMO. The main findings of pooled data can be summarized as follows: (1) there was a large heterogeneity in the development of heart failure—AMI model with LAD occlusion was preferentially used and experiments were mostly performed on pigs, (2) materials and methods were poorly reported.

**Main findings**

**Deficiencies in reporting and risks associated**

Pre-clinical studies in large animals require consistent and reproducible methods in order to ensure comparability across studies, and ultimately translation into clinical studies. Concerns have been raised regarding the reporting of animal experiments as numerous studies displayed insufficient reporting of methods [37, 38], and our results are in line with those concerns. For example, animals’ characteristics and conditions (e.g., age, feeding management, anesthetic management) may impact animal health or lead to variability in treatment responses [38, 39]. Even more concerning, four studies
failed to report the definition of heart failure used in their experiment. It was also found that serious adverse effects, e.g., premature animal death, were poorly described. It should be taken into account that a limited description of adverse effects poses a serious threat to the validity of experimental studies and constitutes substantial bias in post hoc systematic reviews and meta-analyses [40].

### Table 2 Criteria used to define cardiogenic shock adapted to animal practice

| Dogs          | Clinical criteria | Arterial hypotension* | Pulmonary congestion* | End-organ hypoperfusion* | Low cardiac output* | Elevated filling pressure* | Cardiogenic shock adequately defined? | Cardiogenic shock achieved? |
|---------------|-------------------|-----------------------|-----------------------|--------------------------|---------------------|----------------------------|---------------------------------------|-------------------------------|
| Sakamoto et al. | –                  | –                     | –                     | –                        | No                  | LAP > 10 mmHg               | No                                    | N/A                           |
| Kawashima et al. | –                 | –                     | –                     | –                        | –                   | No                         | No                                    | N/A                           |
| Yu et al.      | No predefined criteria | –                     | –                     | –                        | No                  | No                         | No                                    | N/A                           |
| Ox            | Segesser et al.   | “pressure drop”        | –                     | –                        | –                   | –                          | No                                    | N/A                           |
| Pigs          | Møller-Helgestad et al. | –                 | –                     | SvO2 ≤ 35%              | +                   | –                          | Yes                                   | Yes                           |
|              | Ostadal et al.    | –                     | –                     | –                        | +                   | –                          | Yes                                   | Yes                           |
|              | Simonsen et al.   | +                     | –                     | –                        | +                   | Yes                        | Yes                                   | No                            |
|              | Janak et al.      | +                     | –                     | –                        | +                   | Yes                        | No                                    | No                            |
|              | Vanhuyse et al.   | +                     | –                     | +                        | +                   | Yes                        | Yes                                   | Yes                           |
|              | Esposito et al.   | No predefined criteria | –                     | –                        | –                   | –                          | No                                    | N/A                           |
|              | Hala et al.       | Cardiogenic shock not studied | –                     | –                        | –                   | –                          | N/A                                   | N/A                           |
|              | Itch et al.       | No predefined criteria | –                     | –                        | –                   | –                          | No                                    | N/A                           |
|              | Ostadal et al.    | +                     | –                     | +                        | –                   | –                          | Yes                                   | Yes                           |
|              | Brehm et al.      | +                     | –                     | –                        | –                   | +                          | Yes                                   | No                            |
|              | Kajimoto et al.   | No predefined criteria | –                     | –                        | –                   | –                          | No                                    | No                            |
|              | Zhu et al.        | +                     | –                     | –                        | –                   | –                          | Yes                                   | No                            |
|              | Bartoli et al.    | –                     | –                     | Reduction of SvO2 by 10% | +                   | Elevation of LAP ≥ 5 mmHg | Yes                                   | Yes                           |
| Sheep        | Sauren et al.     | –                     | –                     | –                        | –                   | –                          | No                                    | N/A                           |
|              | Naito et al.      | MAP reduction > 20 mmHg | –                     | –                        | +                   | LAP increase > 10 mmHg     | Yes                                   | Yes                           |

Data were divided into clinical and hemodynamic variables with “+” indicating the criterion was met and “−” indicating the criterion was not met. When a criterion was correctly defined but met a different threshold, we considered the criterion to be met and wrote the precise threshold used in the study. We considered that a study had defined cardiogenic shock adequately if (i) it was consistent with the guidelines in force at the time of the experiment; (ii) it used a combination of two criteria present in any guidelines including at least one clinical criterion; or (iii) it used one criterion in the context of acute heart failure induction. We considered that a study had achieved cardiogenic shock if those criteria were met during the experiment. Otherwise, it was considered as “acute heart failure without cardiogenic shock”.

LAP left atrial pressure; MAP mean arterial pressure; SvO2 venous saturation of oxygen

*Criteria from SHOCK and IABP-SHOCK II Trial and NICE Clinical Guidelines

*Altered mental status, cold/clammy skin and extremities, urine output < 0.5 mL/kg/h, pH < 7.35, elevated serum creatinine, lactate > 2.0 mmol/L, SvO2 threshold based on criteria from SHOCK and IABP-SHOCK II Trial, NICE, and ESC Clinical Guidelines

*Cardiac index (CI) ≤ 2.2 L/min/m² or cardiac output (CO) < 3.5 L/min or > 20% drop in CO. Based on criteria from SHOCK and IABP-SHOCK II Trials and ESC Clinical Guidelines

*Pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg or increased left atrial pressure (LAP). Based on criteria from SHOCK Trial and ESC Clinical Guidelines
**Heterogeneity in heart failure models**

With regard to the development of heart failure, it should be mentioned that the most common indication of VA-ECMO is cardiogenic shock refractory to medical therapy [41]. Thus, to translate animal data to clinical practice, the induced heart failure had to be severe. In our analysis, we used rather broad criteria to define cardiogenic shock, i.e., features described in three different guidelines and a reduction in mean arterial pressure and cardiac output. Irrespective of our wide-ranging criteria, seven out of the 18 studies investigating acute heart failure failed to meet those diagnostic criteria and were considered as “acute heart failure without cardiogenic shock.” Regarding the models used, one should be careful when using the term “acute myocardial infarction” as the methods used behind this term were shown to be variable—from sequential ligation of left circumflex side branches to total proximal irreversible LAD ligation which may impact the severity and predominance of ventricular dysfunction.

**Heterogeneity in ECMO support**

There is a growing consensus that a more accurate terminology is needed in the field of ECLS. As such, it has recently been asserted that “VA-ECMO” should not be applied as an umbrella term for various situations but should be used only to denote the circulatory element of extracorporeal organ support (ECOS) [42]. In the same way, the Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI, USA) has recently published an international multidisciplinary standardized nomenclature for definitions and terminology for ECLS [9].

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**Fig. 2** Representation of the five heart failure models that were used in our review. From left to right: ventricular pacing, myocardial hypoxia (through lowering of mechanical ventilation or perfusion of desaturated blood in the coronary arteries), CO poisoning, myocardial infarction, and drug-induced heart failure. CO, carbon monoxide; FiO₂, inspired fraction of oxygen; Vt, tidal volume. Images were obtained from https://smart.servier.com and are available under a creative commons license.
In our review, we highlighted the poor reporting of, and the lack of a unified terminology for, even very basic data: access (percutaneous versus surgical), priming solution, anticoagulation target, or cannula size.

### Table 3: Detailed characteristics of heart failure model

| Study            | Heart failure | Injury model          | Procedure description                                                                 | Complications                  |
|------------------|---------------|-----------------------|---------------------------------------------------------------------------------------|--------------------------------|
| Sakamoto et al.  | Acute         | Myocardial infarction | LAD ligation with suture                                                              | –                              |
| Kawashima et al. | Acute         | Myocardial infarction | LAD ligation (sequential from distal to proximal every 10 min)                        | Death from VF (3 out of 6)      |
| Yu et al.        | Acute         | Myocardial infarction | LAD ligation (7 min)                                                                  | –                              |
| Segesser et al.  | Acute         | Pacing                | External stimulation to induce VF                                                     | –                              |
| Møller-Helgestad et al. | Acute     | Myocardial infarction | LMCA injection with alcohol microspheres                                              | Death from VF (2 out of 14)     |
| Ostadal et al.   | Acute         | Myocardial hypoxia    | Switch mechanical ventilation to 5 breaths/min, 100 mL V₅ and FIO₂ 21%                | –                              |
| Simonsen et al.  | Acute         | Carbon monoxide poisoning | Carbon monoxide administration                                                  | Cardiac arrest (6 out of 12) leading to death (n = 5) |
| Janak et al.     | Acute         | Myocardial infarction | LAD and LCx occlusion by balloon inflation (5 min, echo-guided)                      | –                              |
| Vanhuysse et al. | Acute         | Myocardial infarction | LAD ligation (proximal) with tourniquet (60 min)                                     | –                              |
| Esposito et al.  | Acute         | Myocardial infarction | LCx occlusion (proximal) by balloon inflation (30 mins)                              | Death from VF (2 out of 10)     |
| Hala et al.      | Acute         | Pacing                | Ventricular pacing (200 bpm)                                                         | –                              |
| Itoh et al.      | Acute         | Pacing                | Direct 3.5 V alternate current to induce VF                                            | –                              |
| Ostadal et al.   | Acute         | Myocardial hypoxia    | LAD or LCx perfusion with venous blood                                                | VF (2 out of 5)                 |
| Brehm et al.     | Acute         | Drug-induced (Esmolol) | Esmolol bolus bolus at 2 mg/kg into the LA                                            | –                              |
| Kajimoto et al.  | Acute         | Myocardial infarction | LAD ligation with sutures (10 min)                                                    | Death (2 out of 19)             |
| Zhu et al.       | Acute         | Myocardial infarction | LAD ligation between diagonal branches                                                | Death (2 out of 24)             |
| Bartoli et al.   | Acute         | Myocardial infarction | LAD ligation (sequential)                                                            | Death from arrhythmias (21 out of 47) |
| Sauren et al.    | Acute         | Myocardial infarction | LCx (or side branches) ligation                                                       | “Unstable” (3 out of 7)         |
| Naito et al.     | Acute         | Drug-induced (Esmolol) | Esmolol bolus at 2 mg/kg into the LA and drip infusion (50 to 500 mg/kg/min)         | –                              |

_bpm_ beats per minute; LAD left anterior descending coronary; LCx left circumflex coronary; LMCA left main coronary artery; VF ventricular fibrillation

*A delay of 4 to 8 weeks was respected in order to obtain clinical signs of heart failure*
| Study            | ECMO type | ECMO type | ECMO equipment | Oxygenator | Canula size (Fr) | Flow     | ACT target (s) |
|------------------|-----------|-----------|----------------|------------|------------------|----------|----------------|
| Sakamoto et al.  | Peripheral| Vjr-Afr   | ND             | No         | CBBPX-80        | ND       | ND             |
| Kawashima et al. | CombinationRA-Afr| ND | No | Capiox SP-101 | ND        | 28-10       | 1.5 ± 0.42 L/min | ND   |
| Yu et al.        | CombinationRA-Af | ND | No | Bio-Source TM200 or T-PLS | ND | 21-17 | 75 mL/kg/min | 400-500 |
| Ox               | Segesser et al. | Combination | Vfr and P − A_{CE} | N/A | N/A | ND | ND |
| Møller-Helgestad et al. | Peripheral | Vfr-Afr | Percutaneous | N/A | ND | ND | 3.2 to 4.6 L/min | ND |
| Ostdal et al.    | Peripheral | VFr-Af   | Percutaneous   | Yes | Xenios i-cor    | Xenios AG | 21-18 | Controlled* | 200-250 |
| Simonsen et al.  | Peripheral | Vjr-Afr  | Surgical       | N/A | Prototype       | Maquet Quadrox D | 21-15 | 3500 rpm | ND |
| Janak et al.     | Peripheral | VFr-Af   | Percutaneous   | No | Levitronix Centrimag | QUADROX | 23-18 | Controlled* | 210-290 |
| Vanhuyse et al.  | Peripheral | VFr-Af   | Percutaneous   | No | Medtronic       | Maquet    | 21-15 | ND | 180-250 |
| Esposito et al.  | Peripheral | VFr-Af   | ND             | No | TandemHeart     | ND       | 21-17 | Controlled* | 300-400 |
| Hala et al.      | Peripheral | VFr-Af   | Percutaneous   | Yes | Levitronix Centrimag | Maquet Quadrox i | 23-18 | Controlled* | 200-300 |
| Itoh et al.      | Central   | RA-AO    | N/A            | N/A | HPM-15          | Excel,ung-prime | 16-10 | 140 mL/kg/min | 160-200 |
| Ostdal et al.    | Peripheral | VFr-Af   | Percutaneous   | Yes | Levitronix Centrimag | Maquet Quadrox i | 21-15 | Controlled* | 180-250 |
| Brehm et al.     | Peripheral | VFr-Af   | Surgical       | No | Levitronix Centrimag | Maquet Quadrox D | 17-19 | Controlled* | ND |
| Kajimoto et al.  | Central   | RA-AO    | N/A            | N/A | Sarns 8000      | Ox-RX05RW | ND | 80-100 mL/kg/min | ND |
| Zhu et al.       | Peripheral | VFr-Af   | Surgical       | No | Biomedicus 550  | ND       | 14-12 | ND | 180-220 |
Table 4: Detailed characteristics of ECMO support (Continued)

| Study          | ECMO type | ECMO equipment | ECMO settings |
|----------------|-----------|----------------|---------------|
|                | Configuration | Cannulation | Technique | Position check | Pump | Oxygenator | Canula size (Fr) | Flow | ACT target (s) |
| Bartoli et al. | Peripheral | Vjr-AO\(^5\) | Surgical | N/A          | Not reported | Capiox SX-10 | 10 to 14-18 to 20 | 0.6-1.16 L/min | > 300 |
| Sheep         | Combination | Vfl-AO | N/A | N/A | MEDOS DP1 | Polystan Safe Maxi Adult | 21-18 to 21 | 2.8 ± 0.9 L/min | > 480 |
| Sauren et al. | Peripheral | Vfl-Afl | ND | No | | | | |
| Naito et al.  | Peripheral | Vj-AO\(^5\) | ND | N/A | EVAHEART | Biocube 6000 | 29-21 | 1.5 ± 0.1 L/min | ND |

Brands used for ECMO consoles, pumps and oxygenators (alphabetically): TandemHeart (Cardiac Assist Inc, USA); QUADROX-i Adult, QUADROX-D and Polystan Safe Maxi Adult (Maquet Cardiopulmonary, Germany); MEDOS DP1 (MEDOS, Germany); Medtronic 550 (Medtronic Inc, USA); HPM-15 and Excelung-prime (MERA, Japan); T-PLS (Twin-Pulse Life Support, SL-1000, New-heartbio Co., Korea); Biocube 6000 (NIPRO, Japan); EVAHEART (Sun Medical Technology Research Corp, Japan); Sarns 8000, CX-RX03RW, CX-RX15W and Capiox SX 10 Oxygenator (Terumo, Japan); Levitronix Centrimag (Thoratec, USA); i-cor and Xenios AG (Xenios AG, Germany)

ACT = activated clotting time; Af = femoral artery; Afl = left femoral artery; Afr = right femoral artery; AO = aorta; asc. = ascending; AR = right atrium (in case of percutaneous cannulation); CAR = carotid artery; ECMO = extracorporeal membrane oxygenation; P = pulmonary artery; RA = right atrium (in case of central cannulation); rpm = rotation per minutes; Vf = femoral vein; Vfl = left femoral vein; Vfr = right femoral vein; Vj = jugular vein; Vjr = left jugular vein; Vjl = right jugular vein
\(^5\) Arterial canula was inserted surgically directly into the abdominal aorta through a graft
\(^6\) For peripheral cannulation, was fluoroscopy or echocardiography used to confirm position of the tip of the canula(s)

*ECMO blood flow was a controlled parameter of the experiment
Propositions for future studies

Choice of animal

Small animals are usually chosen for their accessibility, a lower housing cost, shorter gestation times, and reduced costs for pharmacological treatment, as compared to larger animal models [43]. Even though we could not identify models combining heart failure and ECMO, rodent models supported by ECLS or ECMO have been developed [44–46]. These models should not be abandoned as they can bring preliminary mechanistic results, particularly at cellular or molecular levels, at a lower cost.

Nevertheless, in order to study the effects of VA-ECMO on cardiac failure (especially its physiological impact), considering the currently available technology and the severity of the condition, large animal models are the most adequate. The choice of specific animal species to be used should be based on local resources and laboratory experience. Nevertheless, some specificities are worth mentioning as they might help clinicians and scientists in their choice. In particular, when exploring upper-body blood flow, despite similar cerebral vascularization across different species, the left subclavian artery (LSCA) may be separated from the brachiocephalic trunk at its origin in pigs which may lead to (i) a different arterial curve between left and right upper-body leg, and (ii) a different brain vasoreactivity to laminar flow [47]. Vascular access is also to be mentioned, as sheep femoral arteries form an abrupt angle with the abdominal aorta, thus providing difficult percutaneous access. Finally, ovine and non-human primate models show greater similarity to humans in terms of thrombogenicity mechanisms as compared to dogs or pigs which may impact studies aiming at exploring in vivo impact of ECMO on coagulation [48, 49].

Heart failure model and reporting

Cardiogenic shock in humans is mostly caused by AMI or severe myocardial ischemia (anemia, hypoxia); therefore, the most frequently used animal models are developed through coronary artery occlusions [50]. Nevertheless, as found in our study, these models may produce severe and unpredictable adverse events, such as untreatable hemodynamic instability caused by ventricular arrhythmias. In the specific setting of VA-ECMO research, the extent of ischemic injury should be severe yet controllable in order to develop a sustainable cardiac failure, unless extensive and terminal heart failure is being investigated. Up to today, we have found that such models are limited to the use of esmolol [27, 28] and intra-myocardial injection of ethanol [51]—a recently described and promising method for which data still need to be reproduced. Other methods of inducing heart failure have been proposed, in particular, pressure overload models via cardiac banding-debanding (also known as thoracic aortic compression—TAC), leading to successful, precise, and reproducible results in small animals [52, 53]. The aim of these models’ is slightly different as they study the consequences of an “acute on chronic” heart failure. However, they are relevant for the subpopulation of patients which could undergo ECMO, and the characteristics of precision and reproducibility meet the criteria we identified to study the consequences of VA-ECMO. These models would therefore merit further evaluation, as studies on large animals are currently limited [54].
VA-ECMO settings and reporting

Unless required by the experiment protocol, we believe VA-ECMO settings and more generally hemodynamic support should be standardized to ensure comparability and translation into clinical studies. A clear definition of cardiogenic shock should be provided, and a strategy to support it (fluid therapy, inotropes, and vasopressors) as well as hemodynamic targets (MAP above 65 mmHg with normalization of arterial lactate) as per current guidelines. Once VA-ECMO support has been started, cannulation and settings should be as standardized as possible as per latest guidelines or practice: femoral percutaneous access with arterial tip position confirmation, 60 mL/kg/min of ECMO blood flow, a membrane fraction of oxygen ($FmO_2$) as low as possible in order to reach $SaO_2$ of 92% on the right upper limb, with a sweep gas flow to maintain a stable arterial pH. Ventilation strategy under VA-ECMO is still highly debated, and we do not comment on this since it was not the scope of this review. In Table 5, we propose a minimum dataset based on the latest guidelines [55].

Limitations

Our study has several limitations. Firstly, data extraction into pre-defined categories may result in a simplification of the data presented in the studies reviewed. Secondly, we did not conduct a formal assessment of the risk of bias. Finally, we also excluded studies before 1996 from our analysis and thus, may have excluded viable models.

| Table 5 | Proposed minimum reporting dataset for pre-clinical models of heart failure supported by VA-ECMO |
|---|---|---|
| Dataset | Example items | Notes/criteria proposed |
| 1. Animal | Species, age, sex, housing and husbandry. | Use ARRIVE guidelines [12] |
| 2. Heart failure model | Method of injury including detailed surgical/medical procedure, timing and delay Heart failure/cardiogenic shock definition Heart failure/cardiogenic shock achievement | Use latest guidelines and/or trials adapted to fit with animal practice |
| 3. Hemodynamic | Hemodynamic targets MAP > 65 mmHg, arterial lactate < 2 mmol/L Items mandatory to report: LVOT VTI, LVEF, aortic valve opening, pulse pressure | |
| 4. ECMO type | ECMO configuration Method of cannulation | Peripheral (except in post-cardiotomy setting) Percutaneous femoral access (except in post-cardiotomy setting) |
| 5. ECMO equipment | Pump and oxygenator model Canula model and size Placement confirmation (if peripheral) | Use Maastricht treaty nomenclature [9] |
| 6. ECMO settings | Flow targets Gas exchange targets Anticoagulation treatment and target | 60-80 mL/kg/min $FmO_2$ minimal, sweep gas flow to maintain stable pH |

ECMO extracorporeal membrane oxygenation; $FmO_2$ membrane fraction of oxygen; LVEF left ventricular ejection fraction; LVOT left ventricular outflow tract; MAP mean arterial pressure; $SvO_2$ venous saturation of oxygen; VTI velocity-time index
Conclusion
In this systematic review, an overview of contemporary animal models of heart failure supported by veno-arterial extracorporeal membrane oxygenation was given. There is a large heterogeneity in methodology for heart failure induction, as well as ECMO management reporting. Future studies should aim at minimizing those reporting failures—most likely through the use of a minimum dataset—in order to standardize these pre-clinical experiments and help better translation to clinical studies.

Supplementary information
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Additional file 1.

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